ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 13 (O.S., Vol. XVIII) SEPTEMBER, 1939 NUMBER 3

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Subscription per volume or per annum, net postpaid, $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; $7.50, other countries.

Entered as Second Class Matter at the Post Office at Lancaster, Pa. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph 4, section 538, P. L. & R., authorized October 7, 1936.

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ANNALS OF
INTERNAL MEDICINE

VOLUME 13 SEPTEMBER, 1939 NUMBER 3

THE SIGNIFICANCE OF POST-PRANDIAL GLYCOSURIA IN THE TREATMENT OF DIABETES MELLITUS WITH PROTAMINE ZINC INSULIN *

By I. M. RABINOWITCH, F.A.C.P., *Montreal, Canada*

PROTAMINE zinc insulin is now a definitely established therapeutic agent for the treatment of diabetes mellitus. Judging from the literature, most of the difficulties which were met with, following our first reports [1, 2, 3] of the product now in general use † appear to have been overcome. Theoretically, protamine zinc insulin appeared to be contraindicated in conditions for which quick action is necessary, though this also was contrary to our experiences. Coma is an example. Because of its slow action in ordinary amounts, it was repeatedly stated in the literature that protamine zinc insulin is contraindicated in coma. Actually, as we have shown [4] it is not only not contraindicated, but is ideal, when employed under the conditions described.

POST-PRANDIAL GLYCOSURIA

A condition which is not infrequently met with in the use of protamine zinc insulin is *post-prandial* glycosuria; the sugar appears in the urine after meals, but disappears thereafter, so that the following morning the urine is not only free of sugar but the blood sugar is perfectly normal. The excretion of the sugar is preceded by an increase of the sugar in the blood. The duration of the hyperglycemia is, however, variable; the blood sugar may remain high for some hours or return to the normal or nearly normal level within an hour or less. Protamine zinc insulin thus resembles unmodified insulin and the phenomenon is not unlike that observed occa-

* Received for publication August 16, 1938.
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† Though attempts had been made by other workers to prolong the action of insulin and of Hagedorn's protamine insulin, the product upon which these reports were based was that first prepared by Scott and Fisher in the Connaught Laboratories, of the University of Toronto, and supplied to this hospital for clinical trial. It is the protamine zinc insulin which is now in general use.

sionally after ingestion of glucose without insulin.[5] Frank[6] first observed that once sugar appears in the urine it may continue to do so for some time, though the blood sugar has decreased below the generally accepted level of the renal threshold for glucose or has actually reached the normal level.

Post-Prandial Glycosuria and Carbohydrate Tolerance

Ordinarily, when the carbohydrate content of the diet of the diabetic is gradually increased, the appearance of sugar in the urine indicates the limit of carbohydrate tolerance; carbohydrates added to the diet thereafter are excreted practically quantitatively—Allen's Paradoxical Law. A careful investigation of our cases, however, has shown that, in spite of the appearance of sugar in the urine, the carbohydrate content of the diet could be increased without a corresponding increase of glycosuria. An example is shown in table 1. It will be noted that when the total available glucose

Table I

Showing Relationship between Intake and Excretion of Sugar during Treatment with Protamine Zinc Insulin

(Hosp. No. 2706/37)

Date	Diet (Grams)				Urine			Blood Sugar (%)	Body Weight (lbs.)	Protamine Zinc Insulin
	COH	Fat	Prot.	Total G*	Vol.	Sugar %	Sugar Gm.			
Aug. 24/37	250	45	100	310		+		0.285	160	30–0–0
Aug. 25					2950	+		0.107		"
Aug. 26					2450	2.0	49	0.116	157	"
Aug. 27					1925	1.0	20	0.107	156	"
Aug. 28					2050	1.5	31	0.103	158	"
Aug. 29					1925	tr.				"
Aug. 30	300	45	100	360	2100	2.3	49	0.100	157	"
Aug. 31					1950	1.9	37	0.100	158	"
Sept. 1					2750	2.0	55	0.135	156½	"
Sept. 2					1875	2.2	41	0.100	157¼	"

* $G = C + 0.1\,F + 0.58\,P$

of the diet was increased from 310 to 360 grams per day—that is, 50 grams—the average daily excretion of sugar in the urine had increased from 37.2 to 44.3 grams—that is, about 6 grams only—and with one exception only, the blood sugar was still perfectly normal in the fasting state.

Clinically, judging from appearance in general, body weight, activity, etc., the impression has been that this post-prandial glycosuria is not harmful. The findings in general fit in with the observation by Mosenthal[7] that small amounts of sugar may be eliminated in the urine without detrimental results—that glycosuria is harmful only when it is accompanied by polyuria with its resultant dehydration. They also fit in with the observation by Wilder and Wilbur[8] that, even in the difficult cases with the use of prota-

mine zinc insulin, where in spite of intermittent glycosuria which it was necessary to maintain in order to avoid hypoglycemic reactions, the patients seemed to feel healthier and stronger than they had before. They also fit in with an idea which is receiving increasing support, namely, that hyperglycemia is not always harmful. In fact, judging from experiences with diabetics with cardio-vascular disease [7, 9] and experiments in animals [10] it would appear that an increase of sugar in the blood may be beneficial at times—that, within certain limits, it may actually aid the utilization of carbohydrates. In the past, however, judging from our experiences with the metabolism of cholesterol, when our diabetics were treated with high fat diets, hyperglycemia and glycosuria, even when transient, appeared to be harmful.[11, 12, 13] It was, therefore, considered necessary to investigate the cholesterol metabolism in these cases of post-prandial glycosuria following treatment with protamine zinc insulin.

Basis of Use of Cholesterol as an Index of Progress

The cholesterol content of the blood may fluctuate widely in diabetes, not only in different individuals but in the same person at different times. Statistically, however, in the past it was found to be the most reliable index of progress. Joslin and his associates [14, 15, 16, 17] who have had a similarly large experience, and who first suggested this test, still agree with this view.[18] According to McEachern and Gilmour [19] consecutive daily estimations in the same patient give widely varying results, and prove the fallacy of studying the blood cholesterol except under most rigidly controlled conditions. This view, however, was based upon 140 tests in 28 normal subjects; whereas the experiences with diabetics included many thousands of tests during periods of many years. The experiences at The Montreal General Hospital alone include over 15,000 tests on diabetics. The reliability of the test as an index of progress is shown in table 2 in which

Table II

Showing Relationship between Degree of Control of Diabetes and Cholesterol Content of Blood Plasma

Frequency of Glycosuria	Average Plasma Cholesterol (per cent)	
	Adults *	Children †
Urine sugar free: blood sugar normal	0.184	0.176
Urine sugar free: blood less than 0.18%	0.209	0.224
Glycosuria once a month	0.230	0.220
Glycosuria twice a month	0.252	0.286
Glycosuria once a week	0.272	0.260
Glycosuria twice a week	0.288	0.264
Glycosuria daily, but free at times	0.320	0.236
Glycosuria persistent	0.379	0.350

* Rabinowitch, I. M.: Arch. Int. Med., 1929, xliii, 363.
† Rabinowitch, I. M.: Arch. Int. Med., 1929, xliii, 372.

are briefly summarized tables 1 and 2 of a previous report of adults [12] and tables 1 and 2 of a similar report of juvenile diabetics.[13] This study included over 2000 observations in 431 diabetics. The data show the relationship found between the frequency of glycosuria and the cholesterol content of the blood plasma. It will be noted that the cholesterol content of the blood plasma increased as the glycosuria became more frequent. That the differences noted between the average cholesterol values were significant was shown by the ratios of the differences to their "probable errors." For purposes of brevity, the reader is referred to the original papers for the mathematical proof.

Reliability of Plasma Cholesterol with High Carbohydrate-Low Calorie Diet

The above experiences, it should be noted, were prior to 1930 and, therefore, at the time when our diets contained large amounts of fat. Since

Table III

Showing Relationship between Control Index and Cholesterol Content of Blood Plasma in Uncomplicated Diabetes

(1037 Observations in 187 Diabetics)

Group	Control Index (Range)	Number of Cases	Plasma Cholesterol					
			M	σ	PEm	Δ	PEΔ	$\frac{\Delta}{PE\Delta}$
1	−1.00	23	277	58	8.10			
						24	9.8	2.4
2	1.01–1.50	27	253	43	5.54			
						25	6.6	3.8
3	1.51–2.00	40	228	34	3.60			
						18	4.9	3.7
4	2.01–2.50	45	210	34	3.30			
						29	5.8	5.0
5	2.51–3.00	52	181	51	4.73			

Milligrams per 100 c.c. plasma.
M —Mean
σ —Standard deviation.
PEm—Probable error of mean.
Δ —Difference between means.
PEΔ —Probable error of differences.
From: Rabinowitch, I. M.: Ann. Int. Med., 1935, viii, 1436.

then we have used the high carbohydrate-low calorie diet [21] practically exclusively* and one of the characteristics of this diet, as was shown, is an immediate and sustained reduction of the plasma cholesterol. Therefore, before the cholesterol content of the blood plasma may be used to test the

* A number of changes have been made since our first report of this diet in 1930, in order to make it more attractive—increase of meat or fish, frequent feedings, etc.—but there have been no radical changes; the average diet still consists of, approximately, 260 grams of carbohydrate, 45 grams of fat and 100 grams of protein.

significance of the post-prandial glycosuria noted with protamine zinc insulin, it must be determined definitely whether plasma cholesterol is still a reliable index of progress. That it is, was clearly shown in a study by the writer [22] of 1037 observations in 187 diabetics who had no complications which are known to either increase or decrease the cholesterol content of the blood plasma, independent of the degree of control of the diabetes. A summary of these experiences is shown in table 3 which is a reproduction of part of the previously published table. In this investigation, the cholesterol content of the blood plasma was compared with the degree of control of the diabetes and the latter was judged by the Control Index.†

Reliability of Plasma Cholesterol with Protamine Zinc Insulin

A possibility which had to be considered was that protamine zinc insulin may, per se, influence the metabolism of cholesterol and thus limit the value of the test as an index of progress. That protamine zinc insulin has not altered the reliability of this test is shown in tables 4 and 5.

Table IV

Showing Relationship between Control Index and Cholesterol Content of Blood Plasma in Diabetics Treated with Protamine Zinc Insulin

(1000 Observations in 161 Cases)

Group	Control Index (Range)	Number of Cases	Plasma Cholesterol					
			M	σ	PEm	Δ	PEΔ	$\frac{\Delta}{PE\Delta}$
1	–1.00	0						
2	1.01–1.50	8	247	38	9.00			
						35	10.0	3.5
3	1.51–2.00	19	212	26	4.51			
						30	7.3	4.1
4	2.01–2.50	41	182	41	5.85			
						9	9.0	1.5
5	2.51–3.00	93	173	32	2.00			

Milligrams per 100 c.c. plasma.
M —Mean
σ —Standard deviation.
PEm—Probable error of mean.
Δ —Difference between means.
PEΔ —Probable error of differences.

Table 4 shows the relationship found between the Control Index and the cholesterol content of the blood plasma. The data clearly indicate that protamine zinc insulin has not altered the reliability of the cholesterol content of the blood plasma as an index of progress, though the average values are lower than those shown in table 3 with similar disturbances of the diabetes.

† The Control Index is used in this Clinic as a quantitative guide of the degree of control of the diabetes. The details of this Index were dealt with in a previous communication.[22]

TABLE V

Showing Relationship between Cholesterol Content of Blood Plasma and Insulin Dosage after One Year of Treatment with Protamine Zinc Insulin

Group	Control Index		Number of Cases	Average Chol. %	Insulin Dosage					
					Increased		Stationary		Decreased	
	Range	Average			No.	%	No.	%	No.	%
1	1.01–1.50	1.35	8	0.247	6	75.0	2	25.0	0	0
2	1.51–2.00	1.86	19	0.212	11	57.9	7	36.8	1	5.3
3	2.01–2.50	2.21	41	0.182	8	19.5	26	63.4	7	17.0
4	2.51+	2.63	93	0.173	5	5.4	31	33.3	57	61.3

Table 5 is a confirmation of the results shown in table 4. It shows the relationship found between the cholesterol content of the blood plasma and insulin dosage in the same cases. The data include 161 diabetics treated with our high carbohydrate-low calorie diet and with protamine zinc insulin for an average period of one year. It will be noted that of the 93 patients whose average plasma cholesterol was perfectly normal, namely, 0.173 per cent, 57—an incidence of 61.3 per cent—were able to reduce their insulin dosage; whereas, of the 41 whose average plasma cholesterol was just at the upper level of normality, namely, 0.182 per cent, 7 only—that is, 17 per cent—were able to reduce their dosage, and of the 9 whose average plasma cholesterol was definitely above the normal, one only was able to reduce the insulin dosage.

POST-PRANDIAL GLYCOSURIA AND PLASMA CHOLESTEROL

Having found that the cholesterol content of the blood plasma is a reliable index of progress with the combined use of the high carbohydrate-low calorie diet and protamine zinc insulin, it is now possible to determine the effects of the post-prandial glycosuria with a reasonable degree of accuracy. For this purpose, the last 1500 plasma cholesterol determinations were correlated with the blood and urinary sugar findings. A summary of the data is shown in table 6.

TABLE VI

Showing Relationship between Hyperglycemia and Cholesterol and Absence of Relationship between Transient Glycosuria and Cholesterol

	Blood sugar normal			Blood sugar increased		
	All Values	No Glycosuria	Transient Glycosuria	All Values	0.121 to 0.180	0.181+
Number	811	507	304	689	427	262
Average Cholesterol (mg. per 100 c.c.)	176	174	179	191	186	199

It will be noted that the 1500 observations are divided into two groups, namely (a) those with normal blood sugars and (b) those in which the sugar content of the blood was increased. The data, thus divided, show that the average cholesterol content of the blood plasma in the group with normal blood sugars was 0.176 per cent; whereas in the group in which the blood sugars were increased it was 0.191 per cent. The difference is not very great. That the plasma cholesterol reflects the degree of control of the diabetes, is more definitely shown by dividing all of the data of the second group into two other groups, namely: (a) Those in which the bloods were moderately hyperglycemic only (blood sugar range = 0.121 to 0.180 per cent); and (b) those in which the bloods were markedly hyperglycemic (blood sugar = 0.181 per cent or more). With this division, it will be

TABLE VII

Showing Statistical Proof of the Harmlessness of Post-Prandial Glycosuria in Diabetics Treated with the High Carbohydrate-Low Calorie Diet and Protamine Zinc Insulin

	Blood sugar normal		Blood sugar increased	
	No Glycosuria	Glycosuria	0.121 to 0.180	0.181+
Number of tests	507	304	427	262
Average plasma cholesterol *	174	179	186	199
σ	47	61	53	67
PEm	1.40	2.35	1.72	2.78
Δ	5		7	13
PEΔ	2.73		2.91	3.34
$\frac{\Delta}{PE\Delta}$	2.8		2.4	3.9

σ = Standard deviation.
PEm = Probable error of mean.
PEΔ = Probable error of difference.
Δ = Difference between means.
* mg. per 100 c.c.

noted that whereas with the normal blood sugars, the average cholesterol value was 0.176 per cent with the moderate hyperglycemia, it was 0.186 per cent and with marked hyperglycemia it was 0.199 per cent.

In view of the above findings, the *normal* blood sugar values were divided into groups, namely, (a) those with and (b) those without post-prandial glycosuria. It will be noted, however, that with this division, the average cholesterol content of the blood plasma was practically the same, namely, 0.174 and 0.179 per cent respectively.

The significances of the differences between the different averages were judged by their "probable errors." The results are shown in table 7. Briefly, they indicate that, whereas there were significant differences between the cholesterol values of those with and those without an increase of blood

sugar and between those with moderate, and those with marked, hyperglycemia, the difference between the average of those with and those without post-prandial glycosuria, but with normal blood sugars, was not significant. The conclusion, therefore, is that the post-prandial glycosuria in diabetes treated with protamine zinc insulin, when associated with a perfectly normal blood sugar in the fasting state, is not harmful. This conclusion, it should be pointed out here, is based entirely upon use of protamine zinc insulin with our high carbohydrate-low calorie diet. It may or may not apply to other diets.

Since this paper was submitted for publication, a similar analysis was made of another 1500 cholesterol determinations and the results were essentially the same. The data fit in with the lesser importance which is now being attached to glycosuria in the diabetic than in the past. Himsworth,[23] for example, now restricts the "post-absorptive glycosuria within reasonable limits" and Priscilla White [24] no more insists upon sugar-free urine in the treatment of juvenile diabetics. In fact, Dr. White now [25] regards the diabetes under good control though as much as 10 to 20 per cent of the total carbohydrate of the diet may be excreted in the urine. This, according to some of the diets used by Dr. White, amounts to 20 to 40 grams of sugar. The explanation of the discrepancy between past and present practices is, I believe, to be found in the change of the diet of the diabetic—more liberal use of carbohydrate and reduction of fat. An analogy is found in the experiences with protein. With the old low carbohydrate-high fat diets large quantities of protein were avoided because they were known to have been harmful; whereas, with our high carbohydrate-low calorie diet, we have not only found liberal amounts of protein not harmful but, actually, beneficial; they promote skeletal growth in the child and improve health in general in the adult. Very few of our adult diabetics now receive less than 100 grams of protein a day. The ability to tolerate liberal amounts of protein is due to the increase of carbohydrate and reduction of fat in the diets; the diets no longer approximate the exclusively fat-protein diet which was known to convert a mild into a severe diabetes in man and to cause complete diabetes in the partially depancreatized animal.

This work was done with the aid of a Grant from Mr. J. C. Newman, President, and Mr. Julian C. Smith, member of the Board of Management, of The Montreal General Hospital.

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A FAMILY OUTBREAK OF TYPE V PNEUMOCOCCIC INFECTIONS: CLINICAL, BACTERIOLOGICAL AND IMMUNOLOGICAL STUDIES *

By JOHN W. BROWN, and MAXWELL FINLAND, F.A.C.P.,
Boston, Massachusetts

TILGHMAN and Finland [6] recently reported 33 groups of multiple contact cases of pneumococcic infections, including five family groups, in which bacteriological and immunological studies were made.[3] The present paper concerns similar observations in another family consisting of 11 members, 9 of whom had infections with type V (Cooper [1]) pneumococci and a tenth member carried the same organism while apparently remaining free of symptoms. Early in the course of this investigation, type VI pneumococci were cultured from the throat of one individual in the same family and pneumococci of this type were subsequently isolated from the throats of six of the 11 members, none of whom had infections attributable to this organism. During the fourth week of this study, beta hemolytic streptococci were cultured from the throats of seven members of the family, including two with tonsillitis and one with a sore throat.

MATERIALS AND METHODS

The course of the outbreak and the factors determining its spread were studied by observation of the three members of the family who were admitted to the hospital and by periodic visits to the home. The epidemiologic data were obtained with the assistance of Dr. C. D. Cunningham, epidemiologist for the State of Connecticut, while he was attending the Harvard School of Public Health. Cultures were made of sputum, pharyngeal swabs and aural discharges, and blood samples for serological studies were obtained from the various members of the family. The bacteriological studies were concerned mainly with the isolation and identification of pneumococci and their types. The immunological studies consisted of tests for agglutinins and for mouse protective antibodies in the serum. The methods employed and the organisms used for the serological tests were similar to those used in previous studies.[2, 3]

CLINICAL, BACTERIOLOGICAL AND IMMUNOLOGICAL OBSERVATIONS

The occurrence of respiratory tract infections (including middle ear infections) and the results of the bacteriological studies are represented graphically in figure 1. These data and the results of the immunological tests are listed in table 1. The findings may be summarized briefly.

* Received for publication May 28, 1938.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston.

This investigation was aided, in part, by a grant given in honor of Francis Weld Peabody by the Ella Sachs Plotz Foundation.

This work was carried out with the technical assistance of Mrs. Mildred W. Barnes.

Three children of family H. were admitted to the Boston City Hospital on April 27, 1937. Each of these three children was found to have lobar pneumonia involving the right lower lobe; each had or soon developed bilateral suppurative otitis media; and type V pneumococci were isolated from the purulent aural discharge and from the sputum or throat culture in each case. While the children were in the hospital, and again after they were discharged, visits were made to the home of this family. Careful inquiries

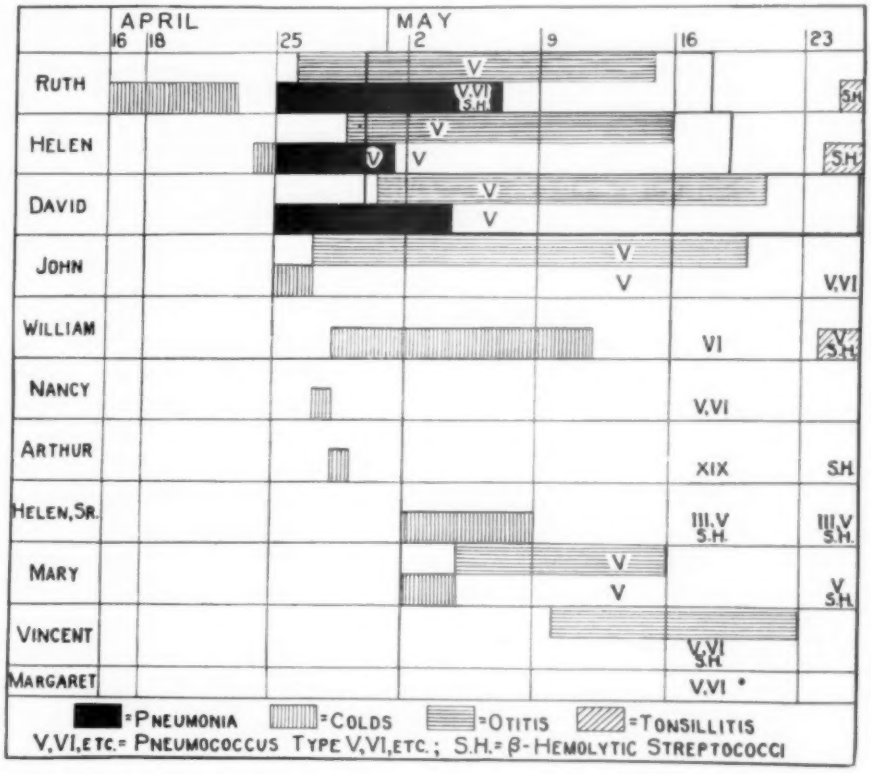

FIG. 1. Spread of respiratory infections in family H. The heavier lines enclose the interval of hospitalization.

were made concerning respiratory tract infections in all the members of the family, cultures were made of the throats and of any aural discharge observed, and blood was taken to determine whether specific antibodies had developed against any of the types of pneumococci encountered.

No other cases of pneumonia developed in the family, but three other siblings became ill with otitis media and, in each instance, type V pneumococci were obtained on culture from the aural discharge or from the throat or from both. Pneumococci of this type were also isolated on one or more occasions from the throats of both parents and from two other siblings. One of the latter (Nancy) was apparently free of infections

TABLE I

Clinical, Bacteriological and Immunological Data

Name	Age yrs.	Clinical	Bacteriology			Immunology			
			Date	Throat	Ear	Date	Agglutinins‡		Protection
							V	VI	V
Ruth	7	Apr. 16: Coryza, cough 1 week Apr. 25: L. pneum.; crisis May 7 Apr. 26: Bilat. O. M. A.; draining Apr. 27 to May 15 Apr. 29: Adm. B. C. H.; disch. May 18 May 25: Tonsillitis	May 6 May 25	V, VI, S. H. S. H.	V	May 6	1 : 8	0	1,000,000
Helen	15	Apr. 24: slight cough Apr. 25: L. pneum.; serum Apr. 30; crisis May 1 Apr. 29: Adm. B. C. H.; disch. May 19 Apr. 30: Bilat. O. M. A.; draining May 3 to May 16 May 24: Tonsillitis	Apr. 29 May 2 May 25	V* V* S. H.	V	Apr. 30† May 1† May 11	0 1 : 32 1 : 2	0 0 1 : 4	0 10,000,000 1,000,000
David	2½	Apr. 25: L. pneum.; crisis May 4 Apr. 29: Adm. B. C. H.; disch. May 25 Apr. 30: Bilat. O. M. A.; draining to May 21	May 6	V	V	May 6	1 : 2	0	10,000
John	9	Apr. 25: "Cold," fever, in bed to May 9 Apr. 27: Bilat. O. M. A.; draining to May 22	May 13 May 25	V V, VI	V	May 19	1 : 2	0	100,000
William	43	Apr. 28: "Cold," cough—2 weeks May 24: sore throat	May 19 May 25	VI V, S. H.		May 19	1 : 2	0	100,000
Nancy	4	Apr. 28: "Cold," cough, fever—1 day	May 19	V, VI		May 19	0	0	10,000
Arthur	1½	Apr. 29: Fever, malaise—1 day	May 19 May 25	XIX S. H.		—	—	—	—
Helen, Sr.	43	May 2: Cough, fever, headache—1 week	May 19 May 25	III, V, S. H. III, V, S. H.		May 19	1 : 4	0	1,000,000
Mary	18	May 2: Coryza May 6: Left O. M. A.; draining May 7 to May 15	May 13 May 25	V V, S. H.	V	May 19	1 : 2	0	100,000
Vincent	17	May 10: Bilat. O. M. A.; no drainage, well May 22	May 19	V, VI, S. H.		May 19	0	0	100,000
Margt.	12	No illness	May 19	V, VI		May 19	0	0	100,000

Explanation:

* Sputum culture.
† Blood cultures at this time showed no growth.
‡ All sera were tested for type III and type XIX agglutinins and found negative.

Agglutinins: 1 : 2, 1 : 4, etc. = greatest dilution showing floccular agglutination.
Protection: mouse protective antibodies in lethal doses per 0.2 c.c. of serum.
Abbreviations: L. pneum. = Lobar pneumonia.
Bilat. O. M. A. = Bilateral acute otitis media.
Adm. B. C. H. = Admitted to Boston City Hospital.
Disch. = Discharged from Boston City Hospital.
Roman numerals represent pneumococcus types.
S. H. = Beta hemolytic streptococci.

throughout this study, while the other three had had "colds" lasting from one day to two weeks.

The 10 members of this family from whom type V pneumococci were cultured all had high titers of protective antibodies against this organism in their serum. The titers ranged from 10,000 to 1,000,000 fatal doses per 0.2 c.c. of serum. (Helen had a higher titer immediately after specific serum therapy.) In seven of the 10, agglutinins for the same type were also demonstrated in the same samples of serum. The agglutinin titers, except in two of the pneumonia cases, were very low.

In addition to the type V, other types of pneumococci were also cultured. Type VI pneumococci were first isolated from one of the children (Ruth) who had pneumonia. Subsequently, they were obtained from the throats of the father and of four other children. Type VI pneumococci were isolated from a culture of the father's throat taken several days before the one from which the type V organisms were obtained. Type VI pneumococci were found together with type V in John's second throat culture, the first culture having yielded only the latter type. In the other individuals, these two types occurred simultaneously. The relation of the type VI pneumococci to the colds can not be determined from the available data, but this type could not be found in the aural discharge of any of the children with suppurative otitis media. Type XIX pneumococci were cultured from the youngest member of the family, Arthur, who had had a mild infection three weeks previously. Type III pneumococci, together with type V, were isolated from the pharynx of the mother, Helen Sr., on two occasions. Agglutination tests with types III, VI and XIX pneumococci were done in each instance but failed to show agglutinins for these types in any of the sera. No serum was available from the infant, Arthur, who was the only member of the family from whom type V pneumococci were not recovered.

In addition to the pneumococci, beta hemolytic streptococci were cultured from several members of the family. A few colonies of this organism were first noted in the throat culture of Ruth while she was in the hospital. Two weeks later, these organisms were found in small numbers in the pharyngeal cultures of the mother and of one of the brothers (Vincent), but pneumococci predominated in these cultures. On the following week, the hemolytic streptococci were again cultured from the mother and from Ruth, but at this time the latter had tonsillitis and the streptococci were obtained from her in almost pure culture. On the same day, these organisms were cultured for the first time from four other members of the family, including the father, who had a sore throat at the time, and Helen, who had been discharged from the hospital one week previously and had developed tonsillitis since her return home. The strains of hemolytic streptococci were not identified serologically.

TABLE II

Epidemiological Observations

Ruth	Sickly all year. Home from school Apr. 4 to 12 because of cough. Taken to and from school daily by a milk attendant, aged 76 years, who developed "double pneumonia," on Apr. 14 and died Apr. 28 (etiology not determined).
Helen	Slept with David and Nancy until Apr. 27 (with David on Apr. 27). Visited uncle on Apr. 25. Had previously helped care for uncle's children, 3 of whom had otitis media and 2 had mastoidectomies (cultures showed hemolytic streptococci).
David	Slept with Helen. Played with Ruth.
John	Slept with Vincent Apr. 27. Slept with David 1 night.
William	Visited children frequently at hospital, also helped to care for other children at home.
Nancy	Slept with Helen on Apr. 25 and 26.
Helen, Sr.	Nursed all the children while at home. In bed only a few hours during acute stage of "cold," May 2 to 3.
Mary	Slept with Ruth Apr. 25, 26 and 27. On Apr. 25 and May 2, visited uncle (cf. Helen).
Vincent	Slept with John until May 2. Helped care for David and Helen until Apr. 28.
Margaret	Alternately slept with Nancy and David.

EPIDEMIOLOGICAL OBSERVATIONS (TABLE 2)

The degree of contact among the members of this family was found to be extreme, although their living conditions were fairly good and they occupied a comfortable home in the outskirts of the city. Naturally enough, all the younger children played together to some extent. Ruth slept in the same bed with Mary. Both developed acute otitis media and Ruth also developed pneumonia. Helen slept with Nancy and with David during the early part of this outbreak. David also slept with John who, in turn, slept with Vincent on other occasions. John, David, Helen, Mary and Vincent all had otitis, while Helen and Mary acquired lobar pneumonia as well. The parents and the older children waited on the sick members of the family at home and the father visited the children at the hospital regularly. The possibilities of spread by direct contact are evident.

The attempts to elucidate an outside source of infection were not altogether fruitful. Ruth was the first to become ill. She was a deaf mute who attended a special school of 200 pupils, none of whom had had any recent significant respiratory or middle ear infections. However, a woman, aged 70, who acted as a milk attendant at the school developed symptoms of pneumonia on April 14 and died on April 28. She had accompanied Ruth and five other children to and from school daily until April 14. None

of the other children had any illness during April. The onset of the first infection in the family occurred in Ruth on April 16.

The only other reasonably possible outside source of infection was the family of an uncle, three of whose children had had "running ears" for a long time and two had had mastoidectomies. All, apparently, had recovered completely several weeks previous to Ruth's illness. Both Helen and Mary had visited at the uncle's home during the illness of their brothers and sisters, and Helen had previously helped care for some of her cousins when they were ill. The purulent, aural and mastoid discharges of the cousins had been cultured and had yielded hemolytic streptococci. Unfortunately, no bacteriological studies were made of the pneumonia in the milk attendant.

Comment

Previous reports of epidemics of pneumococcus infections have been limited, for the most part, to outbreaks of pneumonia due to type I or type II pneumococci. Schroder and Cooper [5] reported an institutional outbreak during which type V pneumococci were cultured from seven of the nine cases of pneumonia which were investigated. Associated with these pneumonias was a high incidence of "colds" and bronchitis in the institution, but the individuals with these conditions were not studied bacteriologically. Among the cases of multiple contact infections reported by Tilghman and Finland,[6] six groups were due to types of pneumococci segregated by Cooper [1] from among those previously included in Group IV. It is clear from these recent studies and from the present report that pneumococci other than types I and II may be disseminated by direct contact with cases or carriers and produce disease.

One of the families previously reported [3] bears many resemblances to the present one. Family "P." consisted of 13 members, nine of whom either developed pneumonia or otitis media due to type V pneumococci or became healthy carriers of this organism. Subsequently, seven members of this family became carriers of type XXII pneumococci either with or without manifestations of infections due to this organism. Of the nine individuals from whom type V pneumococci were isolated, eight had specific antibodies for this organism in their blood, and these eight included three healthy carriers. Among the seven members from whom type XXII pneumococci were cultured, four had agglutinins for this type; two of the latter were entirely free of infection. One later had tonsillitis and only hemolytic streptococci were cultured from his throat at the time of this infection. The course of this outbreak is shown in figure 2.

The immunological observations in the family reported in this paper and those in the families previously studied [3] indicate that healthy contact carriers of disease producing pneumococci acquire antibodies for the types of pneumococci which they carry. Similar observations were made by Harris and Ingraham.[4] Types of pneumococci which were found without

reference to infections were not associated with homologous circulating antibodies. This was true in the present family, and in the families previously studied.[3]

The etiological relationship of the various pneumococci found in the throat to the "colds" and bronchitis which were observed is difficult to evaluate. Presumably the common colds were due to filterable viruses. The presence of these colds, however, apparently provided favorable conditions for the propagation and rapid dissemination of these pneumococci and probably aided in the establishment of infection with the more virulent

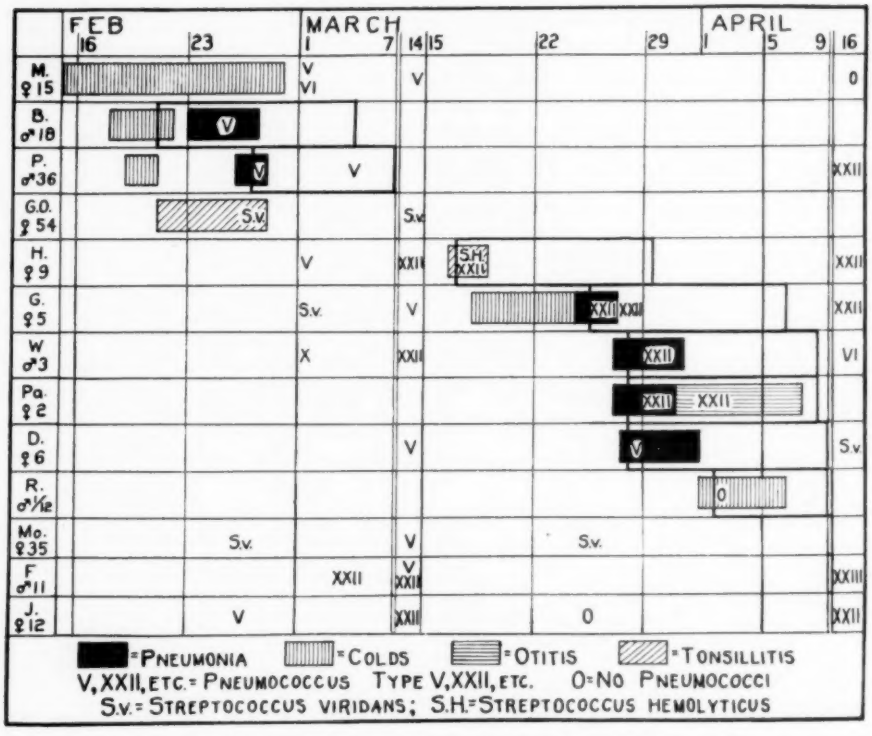

FIG. 2. Respiratory infections in family P. Heavier lines enclose the interval of hospitalization.

type. None of the infections could be definitely attributed to the type VI pneumococci. Previous studies have indicated that the blood of normal children and adults almost universally has marked pneumococcidal activity against type VI pneumococci and the serum is frequently capable of protecting against many fatal doses of these organisms. Such natural antibodies against type V pneumococci are comparatively uncommon.[2]

The sudden and simultaneous outbreak of four cases of pneumonia and otitis media due to type V pneumococci in one family suggests that the organisms in each of these cases were derived from a common source.

Whether this source was a carrier within the family or some case or carrier outside could not be ascertained from the available data. It is possible that Ruth had been exposed to type V pneumococci during her initial "cold" and the others had acquired the organism from her shortly thereafter. The two cases of otitis media that occurred in this family later were probably secondary cases arising out of exposure to the first group. These later cases occurred in the oldest children who presumably had less exposure than the younger ones.

Summary

Clinical, bacteriological and immunological observations were made during an outbreak of "colds," otitis media and pneumonia affecting 10 of 11 members of one family. Type V pneumococci were obtained from the aural discharges in each of the five cases with suppurative otitis media and from the sputum or throat cultures in 10 members of the family, including the only member who remained free of infection. Antibodies for the homologous type were demonstrated in the serum of every member of the family from whom type V pneumococci were cultured, including the healthy contact carrier. During the course of this study type VI pneumococci were also isolated from six members of the family. No infections definitely attributable to this organism occurred, and agglutinins for this type were not demonstrated in any of the sera. Towards the end of the outbreak, hemolytic streptococci were cultured from the throats of seven members of the same family. Of these, two developed tonsillitis and one had a "sore throat."

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ELECTROCARDIOGRAPHIC OBSERVATIONS IN CARDIAC SURGERY *

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PROMPTED by recent developments in cardiac surgery we have investigated, from an electrocardiographic point of view, the effect of surgical manipulation of the heart, both during and after operation. This study is based upon a series of 32 patients all of whom were operated on by Dr. Claude S. Beck. The operations were of two types. The first operative group comprised cases of cardiac anastomosis,[1] for angina pectoris and coronary sclerosis, of which there were 24 cases. The second group were cases of resection of compressive pericardial scars[2] for chronic cardiac compression (Pick's disease), of which there were eight cases, one of which was operated on twice.

METHOD

Electrocardiograms were taken before the operation and at various intervals during the surgical procedure. The three standard leads were taken ordinarily, but in some instances only one lead (usually Lead II) was recorded because of the rapidly progressing surgical procedure. The string shadow was watched during most of the non-recording periods. In the more recent cases accurate time was kept with each record so that correlations with the anesthetist's chart could be made. In all cases the exact step in the operative procedure was noted.

Patients were given morphine and atropine by hypodermic injection from one to one and a half hours before operation. One anesthetist (Mrs. G. Fife) administered the anesthesia in all operations. Nitrous-oxide-oxygen-ether anesthesia was used in 31 operations, supplemented by avertin in six. Cyclopropane with avertin was used twice and procaine (locally) with nitrous-oxide-oxygen-ether anesthesia was used once. In 24 of the cases, an oxygen tent was used postoperatively.

As a preface to this study, the effect of anesthesia in itself must be considered. Kurtz, Bennet and Shapiro[3] found in 109 patients that cardiac arrhythmias were commonly encountered during various non-cardiac operations. The depth and duration of anesthesia had no influence on the arrhythmias. Disturbances of rhythm occurred at all stages of operations and were frequently noted during the preparation of the operative field before the incision was made. Eight of their cases showed delay in A–V conduction; two showed complete heart block; one, paroxysmal auricular

* Received for publication September 19, 1938.
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fibrillation; four, multiple focus ventricular tachycardia; 20, auricular extrasystoles, and 32, ventricular extrasystoles. Patients with abnormal hearts had more changes than patients with normal hearts. The highest incident of arrhythmias occurred with chloroform and the lowest with procaine.

With these findings in mind, we question whether our abnormal electrocardiograms are the result of the anesthetic or whether they may be attributed directly to surgical manipulation of the heart.

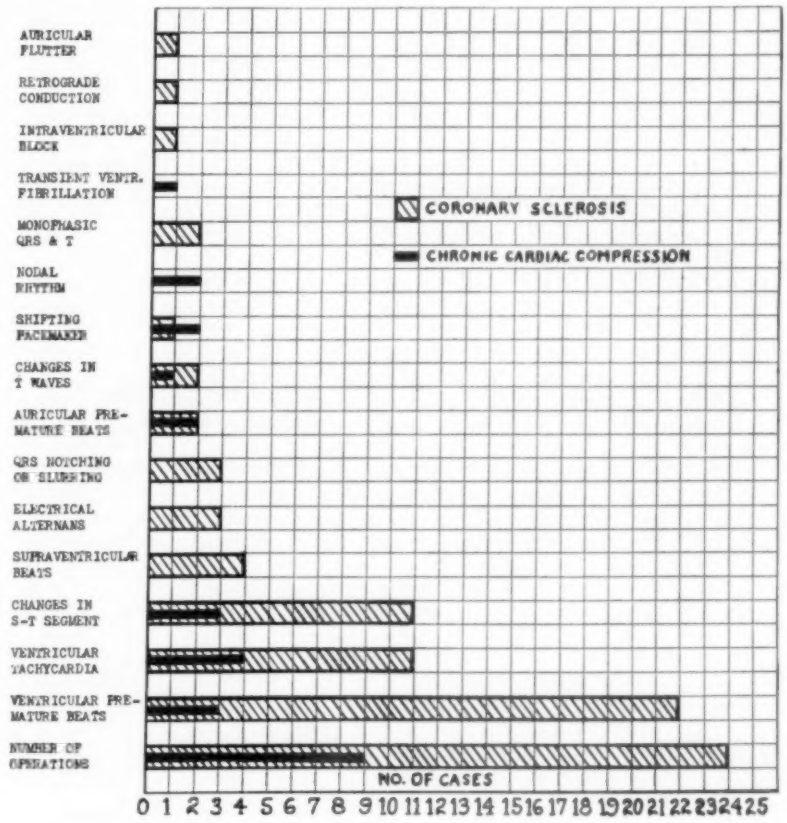

FIG. 1. Abnormal electrocardiographic findings during operation.

Premature beats are the response of cardiac muscle to abnormal irritation or stimulation. In the cases of compression the irritation is due to the separation of scar tissue from the epicardium by the delicate dissection. The irritation is much less than in the case of a cardiac anastomosis where it is due to the roughening of the epicardium with a burr, the insertion of bone meal and the grafting of muscle or fat upon the heart. Figure 1 illustrates all of the abnormal mechanisms found during each type of operation. In the operations for cardiac anastomosis isolated ventricular

premature beats, ventricular tachycardias, and changes in the position of the S–T segment predominate. Ventricular tachycardias include beats of unifocal as well as of multifocal origin (figure 3c). Isolated ventricular premature beats occurred in 22 out of 24 cases (91.7 per cent); there were 11 cases each (45.8 per cent) of ventricular tachycardias and S–T deviations. Of less frequent occurrence were supraventricular beats, auricular extrasystoles, notching and slurring of QRS complexes, changes in the T-waves, electrical alternation (figure 2B), shifting pacemaker, monophasic QRS complexes (figure 8C), intraventricular block (figure 8A), retrograde impulse conduction (figure 2A) and auricular flutter.

During the resection of compression scars, ectopic ventricular beats did not occur as frequently, probably because the irritation was less severe.

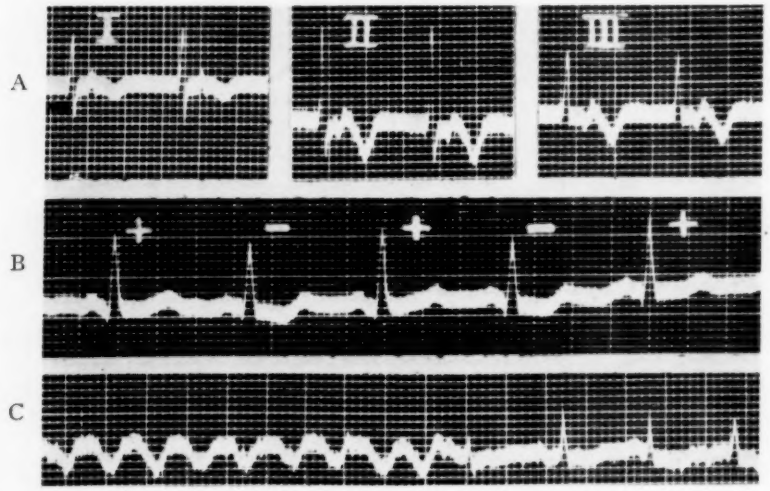

FIG. 2A (Case 26, J. C.). This patient, a man, aged 36, was not given quinidine. Pericardiectomy was performed under gas-oxygen-ether anesthesia. No procaine was used. Leads I, II, and III show a nodal rhythm with retrograde impulse conduction. The P-waves interrupt the S–T segment. This record was taken when the pericardial scar was partly resected and the heart was starting to bulge through the opening. In subsequent records, regular sinus node impulses, at times took over the rhythm.

B (Case 23, C. Z.). This patient, a man, aged 48, was given 13 grains (0.84 gm.) of quinidine preoperatively and a cardiac anastomosis was performed under avertin-ether anesthesia. The pericardium had just been opened and sutured to the chest wall when this record (Lead I) was taken. Procaine had not yet been applied. The R-waves alternate in amplitude. Diphasic T-waves are concordant with the smaller R-waves. Alternation also occurred in Lead II, but not in any of the other records taken on this patient.

C (Case 28, A. P.). This patient, a woman, aged 42, was given 7 grains (0.45 gm.) of quinidine preoperatively and a pericardiectomy was performed under gas-oxygen-ether anesthesia. During a rest period this record (Lead III) of transient ventricular fibrillation was obtained. A sinus rhythm ends the fibrillation abruptly. No procaine was used.

Ectopic auricular beats, shifting pacemaker and nodal rhythm occurred twice in each group. Deviations in the S–T segment occurred in three instances and changes in the T-waves occurred once. Figure 2C shows a transient ventricular fibrillation which occurred in one case.

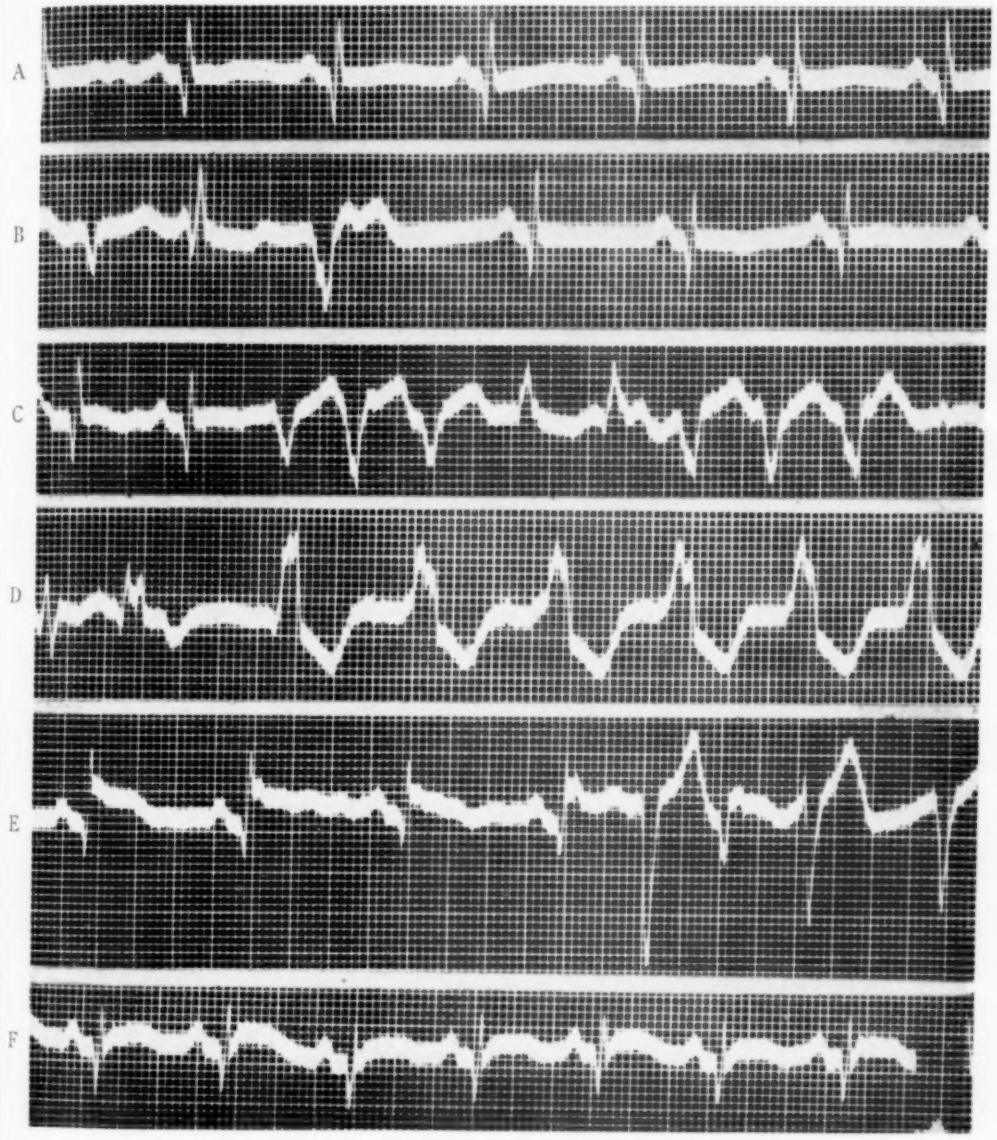

FIG. 3 (Case 24, J. F.). This patient, a man, aged 51, was given 12.5 grains (0.81 gm.) of quinidine preoperatively. A cardiac anastomosis was performed in April 1937 under avertin-cyclopropane anesthesia. All records are of Lead II. This patient had had a coronary occlusion in November 1933 and another in August 1936.

A. Control at 8:58 a.m. before cyclopropane intratracheal anesthesia. The Q_2 and a deep Q_3 (not illustrated) are probably due to a remote cardiac infarct.

B. Pericardium opened, 9:54 a.m. Record shows three ectopic ventricular beats. At 9:58 a.m. 2 c.c. of 5 per cent procaine were applied to the surface of the heart.

C. Posterior parietal pericardium burred, 10:04 a.m. Record shows a ventricular tachycardia due probably to two different foci of impulse initiation. This occurred even though procaine had been applied.

D. Left ventricle anteriorly and laterally burred, 10:09 a.m. Record shows premature ventricular beats from different foci followed by a probable nodal rhythm with intraventricular block.

E. Posterior surface of the heart burred, 10:15 a.m. There are three ectopic ventricular beats. The S–T segment is elevated 4 mm. This may either be a procaine effect or due to myocardial damage.

F. Closure, 10:30 a.m. Record is similar to control except for cove shaped S–T segment. As mentioned under E, this may be due to procaine or myocardial damage.

In the report of 109 non-cardiac operations, extrasystoles of various origins, displaced pacemaker and sinus arrhythmia predominated. According to Wachsmuth and Eismeyer,[4] operative manipulation (non-cardiac in nature) is of much less importance than the anesthetic in the production of cardiac irregularities. They studied the electrocardiograms in dogs and humans during surgical procedures. Hill,[5] Maher, Crittenden and Shapiro [6] as well as Kurtz et al.[3] were also unable to correlate surgical manipulation with cardiac response.

Figures 4A and 4B show the incidence of ventricular premature beats and of ventricular tachycardias during the various stages of the heart operation. In some patients both these mechanisms occurred; in others, neither one. In nine of the coronary cases, ventricular tachycardia occurred only during the period of cardiac manipulation. The latter period is that part of the operation during which the surgeon handles the heart, removes the epicardium or tears it in shreds, inserts bone meal and attaches the grafts. Twenty-one out of 24 (87.5 per cent) of the coronary cases showed isolated ventricular premature beats during this manipulation of the heart. In nine instances the ectopic nature ventricular beats occurred when the parietal pericardium was opened. Figure 3 illustrates typical electrocardiograms taken during the operative procedure. Figure 4C shows that in the coronary patients there is a gradual increase during operation of the other cardiac irregularities. This group of arrhythmias includes auricular and nodal premature beats, auricular flutter, wandering pacemaker, electrical alternation and transient ventricular fibrillation. In addition, notching of QRS and intraventricular block occurred.

Surgical manipulation in the cases of chronic cardiac compression causes few ectopic ventricular beats. The one case showing ventricular tachycardia at the end of the operation had only a few isolated ventricular premature beats during the operation. The compressed heart cases (figure 4C) showed that the other cardiac arrhythmias occurred in seven out of nine cases (77.8 per cent) during the period of cardiac manipulation.

In the operation of cardiac anastomosis, the preponderance of ectopic ventricular beats during the period of cardiac manipulation is obvious (figure 3 and figures 4A and 4B). One may conclude that in the latter operations, isolated ventricular premature beats and ventricular tachycardias are directly related to the manipulation of the heart by the surgeon. Other irregularities may be so related but a larger series of patients must be studied before a positive relationship can be demonstrated. The effect of drugs in preventing these irregularities will be discussed below.

Figure 4D illustrates the changes in the T-waves during operation. These changes consist in the transformation of upright waves to inverted or diphasic waves or vice versa. Once a change occurred it was not replotted in subsequent columns unless there was further change in the way of progression from or regression to the control status. This accounts for the low incidence of T-wave changes during the manipulation period,

whereas in reality, as compared to the control record, there is gradual increase in these changes. They are greatest after the operation has been completed (figure 6) because an inflammatory reaction takes place on the surface of the heart and cardiac damage is being repaired. In only four instances were the T-waves at the end of operation different from those of the control at the start of the operation. Most of the T-wave variations

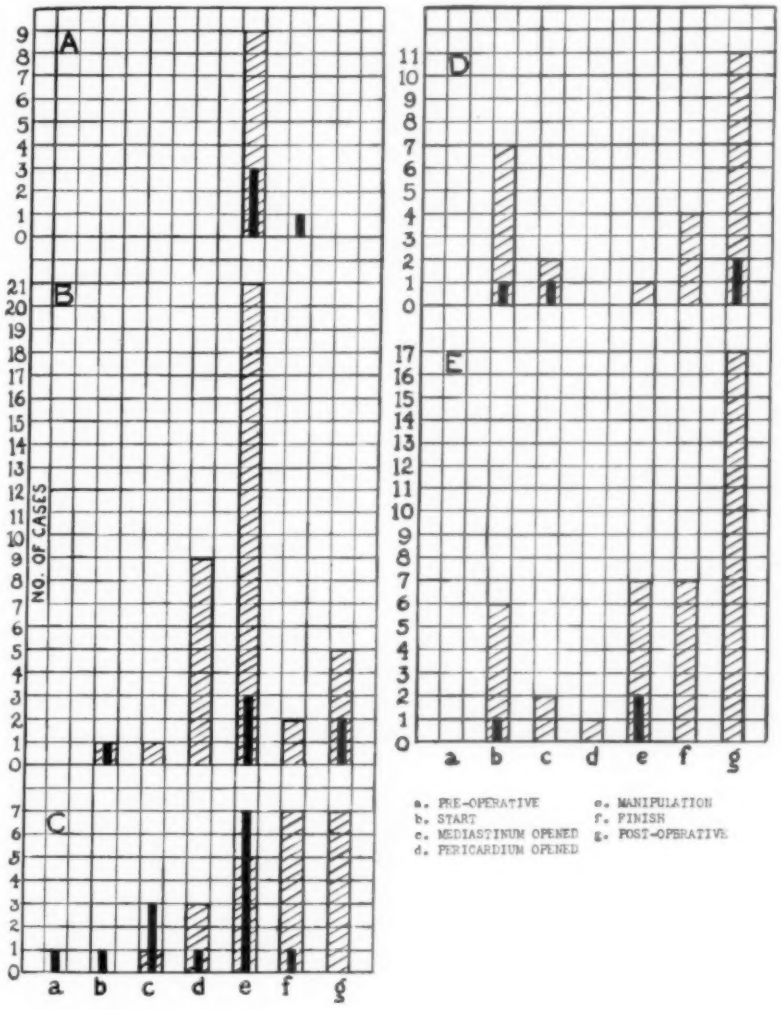

FIG. 4. Incidence of abnormal electrocardiographic findings during the various stages of the operative procedure. Cross-hatched bars indicate the number of cases of coronary sclerosis. Solid black bars indicate the number of cases of chronic cardiac compression.

A. Ventricular tachycardia.
B. Isolated ventricular premature beats.
C. All other changes except D and E.
D. Changes in T-waves.
E. Changes in S–T segment.

are transient; many are associated with S–T changes which take place post-operatively.

Changes in the S–T segment consist in elevations or depressions from the isoelectric level. As in the case of the T-waves, only changes were plotted, as is shown in figure 4E. Experimental[7, 8] as well as clinical[9, 10] experience has shown that changes in the S–T or R–T segments are indicative of ventricular myocardial ischemia or damage. These deviations occur when the heart is roughened by the burr and irritated by the bone meal and grafts. Most changes occur postoperatively (figure 6) and are evidence of an acute myocarditis following operation. It is upon the establishment of this inflammatory reaction with the formation of capillaries, that the anastomosis of the blood supply of the graft with that of the heart in part depends.

The rather frequent S–T deviations at the start of the operation are probably due to anoxemia during the induction of anesthesia and to the added cardiac strain at this time. Six (25 per cent) out of 24 operations for coronary sclerosis and one (11 per cent) out of nine operations for chronic cardiac compression showed S–T variations at the start of the operation.

T and S–T changes during resection of compression scar are infrequent. The hearts in these cases usually have a good blood supply because the patients are younger than the patients with coronary sclerosis. Besides, the surgical trauma is less severe.

Sinus arrhythmias were of frequent occurrence in the records of Kurtz and his associates.[8] We found none. The probable explanation lies in the fact that with rapid heart rates, sinus arrhythmia usually does not occur. In all but four of this series the auricular (sinus node) rate was 100 beats per minute or more. In the four, the auricular rate varied from 71 to 95.

Three patients of the compressed heart group showed no ventricular abnormalities during operation. One of these maintained a regular sinus rhythm with a heart rate of 110 to 120 beats per minute. Another showed no changes in rhythm or contour of the electrocardiographic complexes. The latter two had been given quinidine preoperatively. The third showed auricular extrasystoles, a wandering pacemaker with transient retrograde impulse conduction, S–T_2 depression, but no ventricular abnormalities. (No quinidine had been administered.)

A direct comparison of control records at the start of operation with records at the end showed that 14 out of 33 cases (42.4 per cent) were practically identical (rate excluded). In eight cases (26.2 per cent) the records were similar but not identical due to slight variations in the contour of complexes. The remaining 11 cases (33.3 per cent) showed definite changes as regards notching of QRS complexes, direction of P- and T-waves, position of S–T segment, and nodal and ventricular arrhythmias. These changes in detail are shown in table 1.

TABLE I

Changes in Electrocardiograms at the End of Operation as Compared to Control Records

Case No.	
7, J. H.	$S–T_{1, 2}$ became depressed.
9, G. B.	$S–T_{1, 2}$ depression became isoelectric. Diphasic $T_{1, 2, 3}$ became upright.
10, M. P.	T_1 became inverted.
15, W. R.	Diphasic T_1 became inverted, $S–T_2$ became elevated.
17, A. C.	R_2 became notched.
18, L. H.	Depressed $S–T_2$ became almost isoelectric.
24, J. F.	QRS became notched, $S–T_{1, 2}$ became cove shaped, $S–T_3$ became elevated, T-waves vary with the S–T deviation.
25, J. M.	$S–T_{1, 2}$ became elevated, Inverted P_3 became upright.
26, J. C.*	Normal rhythm became nodal rhythm with retrograde transmission.
28, A. P.*	Isoelectric P-waves became upright.
29, H. T.*	Rhythm of auricular fibrillation became a ventricular tachycardia.

* Cases of chronic cardiac compression.

A comparison of the heart rate as obtained from the electrocardiogram with that as reported by the anesthetist showed wide variations. In most cases the graphic record showed higher rates due to the fact that weak contractions were not transmitted to the peripheral pulse (figure 7). In a few instances, however, the anesthetist's rate was higher. This occurred at very rapid heart rates (135–145).

EFFECT OF PREOPERATIVE MEDICATION

The electrocardiographic changes in conjunction with cardiac operations have just been discussed and the relationship of premature beats and ventricular tachycardia to surgical manipulation of the heart mentioned. As is well known, extrasystoles and ventricular tachycardia may be classed as prefibrillation arrhythmias.

Ventricular fibrillation and coronary disease are closely related. This is probably best shown by the frequent occurrence of fibrillation following experimental as well as clinical coronary closure. Extrasystoles and ventricular tachycardia are also frequently found in patients with acute myocardial infarction. Since these two phenomena are so closely related to the operative procedure in cardiac surgery, the sudden onset of ventricular fibrillation at the operating table as well as post-operatively, is the constant fear of the surgeon. As a protection to the heart against fibrillation the use of quinidine systemically was instituted following observations in the experimental laboratory by Mautz.[13]

Quinidine depresses contractility, prolongs the refractory period, and conduction. The latter effects have long been used to combat auricular fibrillation. Scott [11] by continued administration of quinidine was able to

arrest and prevent ventricular tachycardia. Levine and Fulton [12] report similar findings. Nathanson [14] showed that prefibrillation rhythms induced in elderly persons by intravenous injection of epinephrine could be prevented by the use of quinidine.

Twenty of the cases of coronary sclerosis can be divided into two groups of ten each. Group one received no quinidine preoperatively, and group two did receive quinidine preoperatively. In the latter group procaine hydrochloride was used as a local anesthetic on the heart at operation, but for this study only the electrocardiograms taken before procaine, were used.

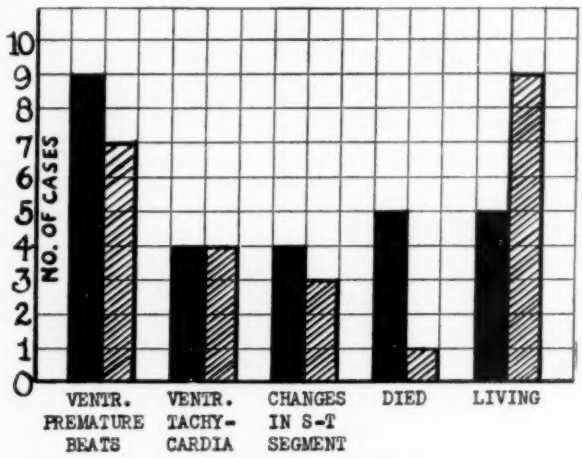

FIG. 5. Abnormal electrocardiographic findings during operation and mortality rate in cases of coronary sclerosis. Solid black bars indicate patients who did not receive quinidine preoperatively. Cross-hatched bars indicate patients who did receive quinidine preoperatively.

Figure 5 shows that there is little difference between the two groups. One cannot say that quinidine, as far as this study is concerned, has a demonstrable effect in preventing prefibrillation arrhythmias. The mortality rate on the other hand appears reduced by the use of quinidine. Is this due to the protection of the heart by quinidine against fibrillation? In this method of establishing a new blood supply to the heart, the magnitude of the operation has been reduced in the more recent cases by the use of a unilateral approach, by the use of smaller grafts, by the use of ground bone instead of extensive excoriation to set up an inflammatory reaction, and also by the use of internal drainage into the left pleural cavity to prevent cardiac tamponade.[16] The rôle that each of these factors plays, as well as the choice of better risk patients must all be considered. As far as the anastomotic operations are concerned each of the above procedures appears to have been an improvement and influential in reducing the risk of operation. Even though we cannot prove by means of electrocardiograms that the number of prefibrillation arrhythmias has been reduced, clinically, there seems to have been a beneficial result.

During the removal of the scar in one patient with chronic cardiac compression, Dr. Beck noticed a transient period of incoördinated ventricular activity which (figure 2C) proved to be a fleeting ventricular fibrillation. This occurred while he dissected a scar from the descending ramus of the left coronary artery which in turn probably reduced the amount of blood going through this artery. This patient had been given 7 grains (0.45 gm.) of quinidine sulphate preoperatively. In another compressed heart case the patient suddenly died seven hours after operation. This

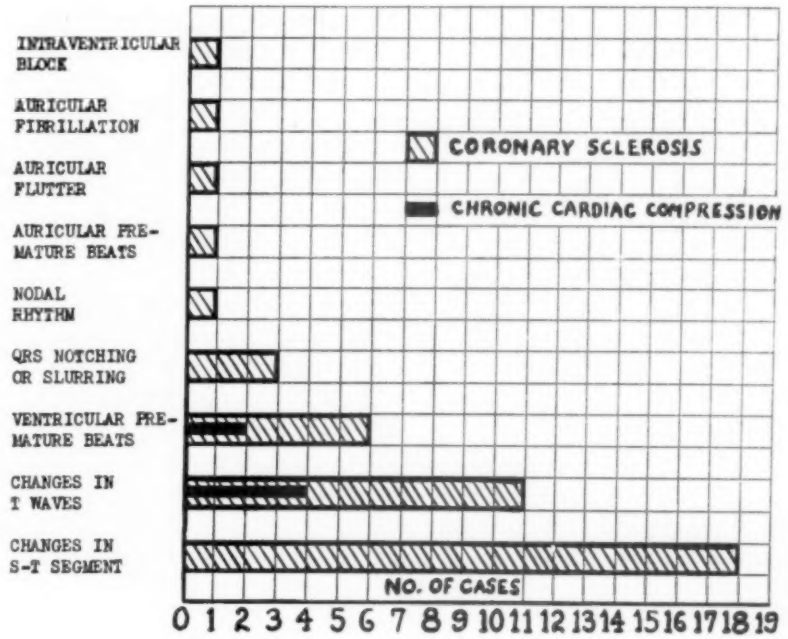

FIG. 6. Abnormal electrocardiographic findings post-operatively.

patient was not given quinidine. Dr. Beck suggested that the cause of death was related to dilatation that occurred when the small atrophic heart was relieved of its compression.

EFFECT OF LOCAL ANESTHETICS APPLIED TO THE CARDIAC SURFACE TO REDUCE CARDIAC IRRITABILITY

Mautz [18] has shown experimentally that the surface irritability of the heart can be decreased by local application of metacaine and procaine. The maximal effect develops within five minutes. On the basis of experimental effects, procaine is used by Dr. Beck in human cases. Two c.c. of a 5 per cent solution are diffused upon the surface of the heart. If this is not effective it may be injected into the cavity of the right ventricle whence it returns to the left ventricle and enters the coronary arteries.

Following the use of procaine in 10 patients, six showed no effect, i.e., there were as many extrasystoles and ventricular tachycardias after application as before. Figure 8B shows a ventricular tachycardia which occurred following the use of procaine. This patient was given a second application, following which no premature beats occurred and a monophasic ventricular complex was produced (figure 8C). These monophasic waves have been described by Mautz [13] as due to the action of the anesthetic on the myocardium.

In three patients following the use of procaine, premature beats ceased. In one patient there were a few isolated premature beats whereas before procaine application there were runs of extrasystoles. The latter four

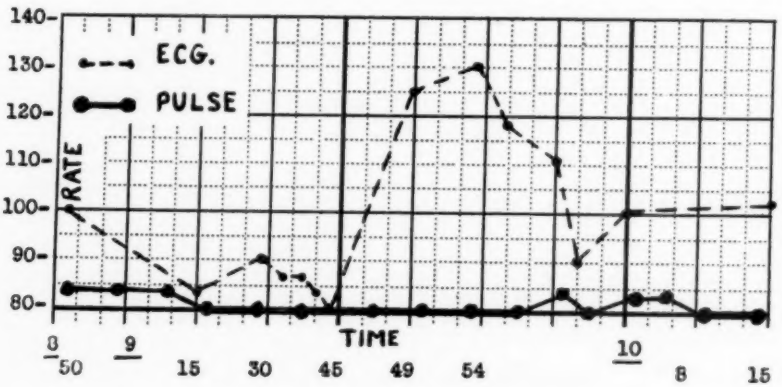

FIG. 7 (Case 23, C. Z.). Comparison of the heart rate as reported by the anesthetist and as obtained from the electrocardiogram. At slower rates the anesthetist's record usually falls below that of the electrocardiographic rate because many of the weaker premature beats are not transmitted to the peripheral pulse.

patients also showed stabilization of the blood pressure level following the use of procaine.

In evaluating the effect of procaine in these few patients, one must consider the different degrees of coronary sclerosis and myocardial ischemia in the various cases; the individual variations in irritability of the heart; the different degrees of surgical trauma, and variations in dosage of procaine. Perhaps a larger dose would have been effective in the six cases which showed no response but we are feeling our way in the use of this drug and we do not want to get toxic effects from large dosage. Conclusions had best be deferred until more cases are studied.

The above discussion shows that the electrocardiograph can point out to the cardiac surgeon those procedures which most disturb the heart and which, therefore, necessitate operative care. Experimentally, quinidine sulphate given systemically lessens the danger of auricular or ventricular fibrillation, and procaine reduces the irritability of the surface layer of myocardium at operation. A method of determining effective dosage is

necessary. For quinidine, Nathanson's [14] method of using epinephrine to induce premature beats and quinidine to counteract this effect, might be used preoperatively in determining the dose. Unfortunately this method is dangerous for cardiac patients and especially in angina pectoris.

For procaine, the dosage is determined at operation. Toxic effects must be avoided.

It has been shown experimentally by Mautz and Beck [15] that procaine introduced into the right ventricle reduces the irritability of the myocardium. This reduction in irritability is useful in throwing the ventricles out of fibrillation. They have worked out a method for defibrillation of the ventricles which in the dog is uniformly successful. This method should find an important place in all operating rooms, not only in heart operations

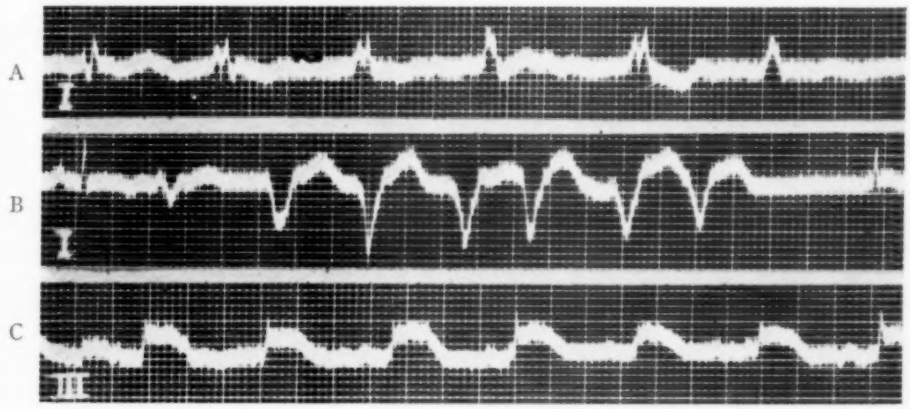

FIG. 8 (Case 25, J. M.). This patient, a man, aged 52, was given 12 grains (0.78 gm.) of quinidine preoperatively and a cardiac anastomosis was performed under avertin-cyclopropane anesthesia.

A. Lead I taken 19 minutes after an application of 2 c.c. of 5 per cent procaine to the heart. The epicardium over the conus arteriosus was being burred. The QRS complexes are notched, vary in contour and in duration (0.08–0.12 sec.). This period of intraventricular block was transient, it had disappeared by the time Leads II and III were taken. There are no definite P-waves and the T-waves vary in direction.

B. Lead I taken 25 minutes after the first procaine application (2 c.c. of 5 per cent) while a second application was being made. This record shows a ventricular tachycardia with beats originating in at least four different foci.

C. Lead III taken about a minute later shows a monophasic type of ventricular complex. This was also seen in Lead II. The S–T segment is elevated from 2 to 3 mm.

but also in operations upon other parts of the body when death suddenly supervenes.

CONCLUSIONS

1. The predominant electrocardiographic abnormalities found during operations for coronary sclerosis are: isolated ventricular beats, ventricular tachycardia, and deviations of the S–T segment from the isoelectric line.

2. During cardiac anastomosis, ventricular premature beats and ventricular tachycardias are directly related to the manipulation of the heart by the surgeon.

3. During the resection of compression scars, ectopic ventricular beats are not as frequent as in cardiac anastomosis because the irritation is less severe.

4. Most of the T-wave variations during cardiac anastomosis are transient; many are associated with S–T changes which take place postoperatively due to an acute pericarditis. T and S–T changes during resection of scars are infrequent.

5. The effectiveness of quinidine in preventing prefibrillation arrhythmias could not be conclusively demonstrated.

6. Procaine hydrochloride, as a local anesthetic applied to the surface of the heart during cardiac operations, may be of some use in preventing prefibrillation arrhythmias.

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THE VITAMIN C REQUIREMENT IN RHEUMATOID ARTHRITIS *

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IN normal healthy individuals the blood serum or plasma level and the urinary excretion of vitamin C are dependent largely upon the dietary intake of the vitamin.[1, 2, 3, 4] It has been shown by van Eckelen [5] and Heinemann [6] that normal adults have a daily requirement of 60 mg. of the vitamin.

The presence of infection is known to increase the requirements for vitamin C.[7] In patients suffering with various forms of infection the level of vitamin C in the blood plasma or serum may be reduced to the level found in patients with scurvy.[7] Under these circumstances the amount of vitamin C required to raise the blood plasma level of the vitamin to that of the kidney threshold and to maintain this degree of "saturation" is many times that accepted as the normal requirement of healthy individuals.[8]

Rinehart [9, 10] has shown that in patients with rheumatoid arthritis there is an apparent vitamin C deficiency as indicated by low concentration of the vitamin in the blood.

The present studies were originally undertaken to determine the incidence of lowered vitamin C content of the blood among patients with rheumatoid arthritis as compared with normal individuals on a similar dietary regime. At the same time information was sought which would indicate whether patients with rheumatoid arthritis had a greater requirement for vitamin C than normal people, and if so whether the satisfaction of such an increased demand would result in clinical improvement.

METHODS

Analytical. The method for the determination of cevitamic acid in the blood plasma is essentially that of Farmer and Abt [11] with slight modifications to prevent oxidation of the vitamin.

Five ml. of venous blood are withdrawn into a tube containing 0.05 ml. of potassium oxalate saturated solution and 1 drop of 5 per cent sodium cyanide solution. The blood is centrifuged and 2 ml. of the plasma are precipitated with 4 ml. of 5 per cent metaphosphoric acid and 4 ml. of distilled water. The protein is removed by either centrifugalization or filtration. Two ml. samples in duplicate of the filtrate are diluted with 3 ml. of distilled water and titrated with 2-6 dichlorophenol-indophenol solution

* Received for publication June 29, 1938.

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which had been standardized on the same day. The first pink color persisting for 30 seconds is arbitrarily taken as the end point.

The determination of cevitamic acid in urine is made according to the method of Taylor et al.[12]

Standard Solutions. The 2-6 dichlorophenol-indophenol solution is made up fresh every week. Approximately 20 mg. of LaMott special indicator solution are weighed into a 100 ml. volumetric flask, dissolved in hot boiled water and diluted to the mark with cold boiled distilled water. (The solution is usually complete, but if any insoluble material is present it should be removed by filtration.) This stock dye solution is then kept in the icebox in a brown glass stoppered bottle.

The working standard is prepared by diluting 10 ml. of the stock dye solution to 100 ml. in a volumetric flask using freshly boiled distilled water.

Standardization of the Dye. Five hundred ml. of 2 per cent metaphosphoric acid are prepared by dilution with boiled distilled water. Approximately 15 mg. of cevitamic acid (Merck's Cebione) are weighed to four places on the analytical balance and transferred to a 100 ml. volumetric flask. The cevitamic acid is dissolved in 2 per cent metaphosphoric acid and diluted to the mark with the same reagent. Ten ml. of this stock standard are transferred to a second 100 ml. volumetric flask and made up to volume with 2 per cent metaphosphoric acid.

One ml. of this working standard is transferred to a titration flask and diluted with 4 ml. of 2 per cent metaphosphoric acid. The mixture is titrated with the dilute dye solution. A blank both for perception of end point and on reagents is made by titrating 5 ml. of 2 per cent metaphosphoric acid.

Clinical Material. The frequency of low levels of vitamin C in the blood plasma was determined from a study of 56 cases of rheumatoid arthritis. The cases were both early and late and had varying degrees of deformity and severity of symptoms. A control group of 12 normal adults living in the hospital on exactly the same diet was studied as a control. An intensive study of vitamin C metabolism was made in ten of the patients with rheumatoid arthritis of long duration. The vitamin C levels in the plasma of these individuals was less than 0.5 mg. per 100 ml. Four of these patients were placed on a vitamin C free diet for a period of from three to four weeks during which time urine analyses for vitamin C were made and periodic estimations of the amount of cevitamic acid in the circulating blood plasma. In addition the response of each of the four patients to the administration of a single oral dose of one gram of cevitamic acid was studied by following the changes in the level of the substance in the blood plasma and urine output of vitamin C. Daily red blood cell counts and hemoglobin determinations were made and the weights of the patients determined at frequent intervals. In addition close check was kept on any clinical changes in the patients including observations on the red blood cell sedimentation rate.

TABLE IA

Cevitamic Acid Level of Blood of 58 Unselected Cases of Rheumatoid Arthritis on Hospital Diet Containing Approximately 80 mg. per Day Cevitamic Acid

Patient No.	Age	Sex	Date	Cevitamic Acid mg./100 c.c. Blood Serum
1	44	female	June 14	2.320
2	27	male	Feb. 18	2.245
3	39	male	Feb. 17	2.023
4	57	female	June 2	1.650
5	40	female	Feb. 12	1.580
6	45	female	June 7	1.260
7	40	female	Feb. 12	1.260
8	49	female	May 6	1.160
9	37	female	Feb. 14	1.110
10	56	female	Feb. 18	1.035
11	29	female	Feb. 14	.950
12	39	female	Feb. 13	.890
13	51	female	May 21	.790
14	27	female	Apr. 27	.730
15	23	female	June 2	.720
16	47	female	Feb. 14	.700
17	50	female	June 18	.678
18	30	male	Apr. 22	.610
19	19	female	June 18	.604
20	62	female	June 18	.562
21	45	female	Apr. 23	.550
22	55	male	Feb. 16	.550
23	29	male	June 18	.548
24	19	male	Feb. 18	.521
25	30	male	May 12	.477
26	35	female	Mar. 10	.475
27	21	male	May 11	.465
28	57	female	Feb. 19	.450
29	13	female	Apr. 22	.429
30	42	female	Feb. 14	.420
31	22	female	Apr. 22	.401
32	23	male	Mar. 20	.393
33	27	female	Feb. 17	.362
34	41	female	May 12	.358
35	27	female	Mar. 20	.350
36	68	male	Apr. 21	.330
37	37	female	June 9	.329
38	51	female	Feb. 18	.329
39	57	female	Apr. 22	.321
40	18	female	Apr. 26	.317
41	61	female	Feb. 14	.302
42	70	female	June 2	.301
43	32	male	Feb. 18	.279
44	21	male	Feb. 20	.268
45	57	male	June 14	.257
46	27	female	May 16	.254
47	41	female	Feb. 18	.253
48	38	male	Feb. 17	.218
49	25	female	Apr. 26	.234
50	47	female	Apr. 27	.214
51	26	male	May 5	.193
52	41	male	May 5	.193
53	28	male	Apr. 27	.172
54	27	female	June 7	.158
55	27	male	Feb. 18	.152
56	17	male	Feb. 18	.152
57	23	female	Feb. 19	.150
58	50	female	May 12	.067

At the end of the control period each of the four patients was placed on a daily intake of 100 mg. of pure cevitamic acid for two weeks and the various observations made during the control period repeated. The patients were then given 200 mg. of cevitamic acid daily by mouth and the observations repeated.

In six of the ten patients the vitamin C free diet was replaced by an ordinary house diet on which the patients were maintained throughout the entire period of observation. In all other respects the studies on these cases were the same as on the other four.

At no time during the observations of any of the ten patients was there any abnormality in the basal metabolic rate and the patients' temperature showed the low fluctuations between 99 and 100° F. typical of the disease in its chronic stage.

Experimental Results

The Incidence of Lowered Blood Plasma Cevitamic Acid Level in Rheumatoid Arthritis. Observations on 24 cases were made shortly after admission to the hospital; the other 31 cases had been in the hospital for from one month to several years before the observations were commenced. The experimental data are summarized in table 1a. In summary, 14 or 25 per cent of these 56 patients showed a cevitamic acid level in the plasma of 0.8 mg. per hundred ml. or higher, which is within the accepted normal range.[4] Nine or 16 per cent had values between 0.5 and 0.8 whereas 33 or 59 per cent had levels of cevitamic acid in the blood plasma below 0.5 mg. per hundred ml. Five of the patients who had plasma cevitamic acid levels above 0.8 mg. had supplemented the hospital diet at the time of this survey with sufficient citrus fruits or orange juice to account for an additional intake of 80 mg. per day of cevitamic acid.

Table Ib

Cevitamic Acid Level of Blood of 12 Normal Individuals Maintained Exclusively on House Diet

Control No.	Age	Sex	Date	Cevitamic Acid mg./100 c.c. Blood Serum
1a	24	female	May 10	2.066
2a	27	female	May 6	1.990
3a	54	female	Mar. 11	1.620
4a	56	female	May 5	1.470
5a	23	female	May 5	1.150
6a	36	male	May 10	1.150
7a	35	male	May 3	.929
8a	49	female	May 6	.832
9a	43	female	May 6	.785
10a	36	female	May 5	.680
11a	21	female	Feb. 16	.560
12a	26	male	May 10	.206

The data obtained on these 12 normal subjects are given in table 1b. Ten or 83 per cent had levels of cevitamic acid in the blood plasma ranging between 0.9 and 2 mg. per hundred ml. Two subjects had values of 0.6 and 0.25 mg. per hundred ml. respectively. The individual with the lowest plasma ascorbic acid stated that he rarely ate fruits or uncooked vegetables included in the diet.

TABLE II

Cevitamic Acid Level of Blood of 29 Cases of Rheumatoid Arthritis after Maintenance on Cevitamic Acid Therapy

Patient No.	Age	Sex	Date	Cevitamic Acid mg./100 c.c. Blood Serum	Cevitamic Acid Excretion in Urine mg./24 Hours	Mg. Cevitamic Acid Orally per Day	No. Days of Therapy
16	47	female	June 2	1.82	137.0	100	12
						200	11
						300	
20	62	female	June 18	.56	17.2	200	16
24	19	male	June 18	1.18	109.6	200	32
25	30	male	June 21	2.13	20.5	200	28
						100	13
27	21	male	June 24	1.32	118.3	200	41
28	57	female	June 24	1.19	87.5	200	14
30	42	female	Apr. 27	1.10	96.0	300	53
31	22	female	June 23	1.27	32.9	200	11
32	23	male	June 2	1.25	100.0	100	11
						200	12
33	27	female	June 22	1.12	104.8	200	39
37	37	female	June 24	1.72	42.0	200	41
38	51	female	June 22	1.83	73.3	100	11
						200	31
39	57	female	June 14	2.16	123.2	200	31
40	18	female	June 23	1.30	100.4	200	30
41	61	female	May 25	1.03	126.0	100	11
						200	12
						300	
42	70	female	June 19	1.71	72.6	200	35
43	32	male	June 18	1.12	144.9	200	33
46	27	female	June 9	1.18	121.4	200	25
49	25	female	June 21	.91	83.3	200	31
50	47	female	June 18	1.19	87.5	200	14
51	26	male	June 18	1.20	124.0	100	11
						200	32
52	41	male	June 26	1.30	36.5	100	11
						200	35
53	28	male	June 21	1.19	35.3	200	28
						100	10
54	27	female	June 21	1.51	148.8	200	14
55	27	male	June 21	1.60	44.2	200	28
						100	13
56	17	male	May 31	.84	139.0	100	11
						200	51
57	23	female	June 3	1.60	90.0	100	11
						200	35
58	50	female	June 18	.96			
10	56	female	June 21	1.30	23.0	100	11
						200	30

The data shown in tables 1a and 1b may be compared with those of table 2 which gives data for cases of rheumatic arthritis after the daily ingestion of vitamin C in amounts varying between 150 and 200 mg. per day. In all of these cases the blood level of vitamin C was normal.

The Vitamin C Requirements of Patients with Rheumatoid Arthritis. The four patients maintained on a vitamin C poor diet showed a daily excretion of vitamin C in the urine below 20 mg. The six patients whose control period was the ordinary house diet showed an excretion which did not exceed 50 mg. per day. During the control period no essential change was observed in the amount of vitamin C in the blood plasma.

The administration of 1 gram of vitamin C to these ten patients was followed by a prompt rise in the level of the vitamin in the blood which returned to the pre-administration levels in 48 hours.

All 10 patients were then placed on a daily intake of 100 mg. of vitamin C per day given in two doses and the urines analyzed daily for vitamin C. Blood samples were taken fasting and before the administration of the vitamin at frequent intervals. With the dosage of 100 mg. there was no significant rise in the blood cevitamic acid level during the two weeks of therapy above that of the control period, nor did the urine cevitamic acid rise remarkably above that obtained for the control period. A typical series of observations on one of these patients is shown in figure 2.

After the patients had taken for two weeks a dosage of 100 mg. per day they were given 200 mg. per day in four doses. Under these circumstances the blood levels rose progressively in 10 to 12 days reaching levels between 1.0 to 1.8 mg. per hundred ml. of blood and remained essentially constant. At the same time the daily urinary excretion increased markedly, ranging from 30 mg. to 100 mg. per day.

In three of the patients the vitamin C administered was increased by an additional 100 mg. The blood level of ascorbic acid did not increase beyond that obtained when 200 mg. were given each day but the daily urinary excretion was increased by 40 to 70 mg.

At the end of the period of 200 mg. level of administration vitamin C was omitted for two days and the response of the patient's blood and urine to a single oral dose of 1 gram was again determined. Table 3 shows a comparison of the response of the patient's excretion of vitamin C following the oral administration of 1 gram of the vitamin during the control period and after the administration of vitamin C. It will be observed that following the generally accepted ideas of saturation with the vitamin that the patients after therapy at a level of 200 mg. per day of the vitamin have become saturated.

These observations would indicate that the requirements of an arthritic individual for vitamin C were between 100 and 200 mg. per day or in other words between two and four times that of a normal individual.

Clinical Effects of Vitamin C in Rheumatoid Arthritis. None of the patients showed symptoms of the type associated with scurvy itself, in spite

TABLE III

Comparison of Amount of Cevitamic Acid Excreted in Urine Following an Oral Dose of 1000 mg. Before and After Cevitamic Acid Therapy in Patients with Rheumatoid Arthritis

Patient No.	Age	Sex	Control Period		Therapy			After Therapy		Per cent of Cevitamic Acid fed to the amount excreted
			Cevitamic Acid mg./100 c.c. blood serum	mg. Cevitamic Acid excreted in 48 hours	Per cent Cevitamic Acid fed to amount excreted in urine	mg. Cevitamic Acid per day	No. of Days	Cevitamic Acid mg./100 c.c. blood serum	mg. Cevitamic Acid excreted in 48 hours	
10	56	female	.320	15.76	1.58	100 200	11 30	1.300	252.64	25.26
16	47	female	.240	72.00	7.20	100 200 300	11 12 8	1.938	466.00	46.60
30	42	female	.700	145.00	14.50	300	16	1.230	460.00	46.00
32	23	male	.190	6.49	.65	100 200	11 11	1.24	523.66	52.37
38	51	female	.380	6.08	.61	100 200	11 12	1.43	356.42	35.64
41	61	female	.380	55.00	5.50	100 200 300	11 12 8	1.15	471.00	47.10
51	26	male	.190	18.00	1.80	100 200	11 14	1.33	178.20	17.82
52	41	male	.110	7.00	.70	100 200	11 8	1.03	515.52	51.55
56	17	male	.140	9.00	.90	100 200	11 15	.85	409.00	40.9
57	23	female	.310	6.43	.64	100 200	11 8	1.23	447.28	44.73

of the fact that many had cevitamic acid levels below that usually present in this disease. In one case, there was a tendency to bleeding gums, but this did not clear up after the blood became saturated with vitamin C. Capillary fragility tests carried out by the method described by Wright and Lilienfeld [13] (i.e. by counting the number of petechiae present in a uniform area on the forearm after 15 minutes of tourniquet pressure held at halfway between systolic and diastolic pressures) showed no significant increase when the plasma level of vitamin C was low, or decrease when the blood was saturated.

After eight months, during which time the patients were given vitamin C daily and their blood known to be saturated with vitamin C, no clinical improvement which could be attributed to the ingestion of vitamin C was observed. Some cases improved during this period, but others continued unchanged or became worse as judged by the condition of their joints, failure to gain weight or hemoglobin, and slowing of the red cell sedimentation rate.

No increase in the red blood cell count was found in any of the patients although occasionally sporadic but slight increases in the reticulocytes were observed.

This study indicates that the ordinary hospital diet was inadequate in its vitamin C content to supply the increased demands of the rheumatoid arthritic and may lead to a general revision of diets in institutions devoted to the care of this disease. Further investigation may discover additional deficiencies in the dietary requirements for other vitamins and essential nutritional substances.

Summary

Seventy-five per cent of 56 cases of rheumatoid arthritis had a subnormal content of vitamin C in the blood. Fifty-nine per cent had levels below 0.5 mg. per 100 ml. These findings are confirmatory of those of Rinehart.[9, 10]

Although some of the patients had had diets containing vitamin C well below the amount usually required for normal people, none of them presented clinical evidence of scurvy.

Patients with rheumatoid arthritis actually have a much greater demand for vitamin C than the normal individual. From a study of 10 patients with rheumatoid arthritis it was shown that these individuals could tolerate an intake of over 100 mg. and usually 200 mg. without marked excretion into the urine.

Following this investigation all patients with rheumatoid arthritis in the Hospital were placed on an intake of 200 mg. of vitamin C per day for 8 months. No improvement has been noted that could be attributed to the effect of the vitamin.

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POSTOPERATIVE PROGRESSIVE EXOPHTHALMOS WITH LOW BASAL METABOLIC RATE*

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More than a century and a half has now elapsed since Parry,[1] in 1786, noted and described exophthalmos in the first classical case of exophthalmic goiter recorded in medical literature. Since then the problem of the etiology and pathogenesis of exophthalmos in association with thyroid disease has been the theme of numerous and intensive studies and investigations—clinical, pathologic and experimental. As the result of these studies, numerous theories of the pathogenesis of exophthalmos have been propounded (table 1), but a complete solution of the problem has not been reached. We have gained considerable knowledge when and how exophthalmos develops in thyroid disorders, but we do not know why it develops. Up to now, we have failed to penetrate into the mystery of the basic cause which is responsible for the pathologic changes which produce the exophthalmos.

We speak glibly of primary toxic goiter, or exophthalmic goiter, and secondary toxic goiter, or toxic adenomatous goiter, as forms of hyperthyroidism. Why, then, does exophthalmos occur very frequently in the primary type and very rarely in the secondary? Why does exophthalmos occur very frequently in mild or moderate cases of primary toxic goiter and very rarely in severe long standing cases of secondary toxic goiter? Why does exophthalmos recede in the majority of cases of exophthalmic goiter after successful thyroidectomy in the early stages of the disease and become severe and progressive in others? Why is exophthalmos absent in some very long standing severe cases of primary toxic goiter before operation, and why does progressive malignant exophthalmos first develop after a successful thyroidectomy with relief of general symptoms and a drop in basal metabolism to normal or minus rate? Regretfully, we have to admit that we have no satisfactory answer to these perplexing questions, for neither do we know the basic cause of toxic goiter nor of exophthalmos in association with goiter.

Nevertheless, despite our failure to discover the basic cause of exophthalmos in thyroid disorders, we have learned a number of facts about its course, pathogenesis and treatment which, if promptly and properly utilized, may be greatly helpful in its practical solution as a therapeutic problem.

Postoperative Progressive Exophthalmos With Low Basal Metabolic Rate

1. *Frequency of Exophthalmos in Primary Toxic Diffuse Goiter and Its Rarity in Secondary Toxic Nodular Goiter.* The frequent occurrence

* Received for publication February 3, 1938.
From the Out-Patient Department, Beth Israel Hospital, New York City.

TABLE I

Theories of Pathogenesis of Exophthalmos in Graves' Disease

Year	Author	Theory of Pathogenesis	Basis for Theory
1834	Dalrymple [2]	Spasm of levator palpebra superioris	The physiological function of the levator palpebra superioris "is to raise the upper lid, to uncover the globe of the eye by drawing the tarsal cartilage beneath the margin of the orbit, and at the same time it slightly protrudes the globe."
1840	Basedow [3]	"Strumous" hypertrophy of retrobulbar cellular tissues	Increase of retrobulbar cellular tissues in a case of progressive exophthalmos with corneal ulceration and destruction of eye.
1849	Begbie [4]	Increase of vitreous humor	Report of a prominent oculist who examined one of Dr. Begbie's patients and found "the sclerotics of both eyes were evidently distended from an increased secretion within."
1849	Cooper [5]	Spasm of levator palpebra superioris; weakness and elongation of eye muscles; retrobulbar venous congestion	Clinical observations and studies.
1852	Bernard [6]	Stimulation of cervical sympathetic	Electrical stimulation of cervical sympathetic in animals produced widening of palpebral fissures, dilatation of pupils and exophthalmos.
1853	Demarres [7]	Hypertrophy of retro-orbital fatty tissue	Observation of one case of exophthalmic goiter with progressive exophthalmos, corneal ulceration and destruction of eye. When the eye was destroyed, "a terrible phlegmon" filled the orbital cavity.
1854	Stokes [8]	Increase of aqueous and vitreous humor	Personal observation of the "clear, transparent and brilliant condition of the eyes free from any signs of 'sanguineous congestion' even in long standing marked exophthalmos." He had known of a case "in which for upwards of a year, the eye was never closed, yet in which no vascularity of the conjunctiva, nor any form of ophthalmia ever occurred."
1856	Taylor [9]	Retro-orbital venous congestion secondary to impeded venous return from head and orbit	In two patients who died of exophthalmic goiter with signs of congestive heart failure, autopsy revealed dilatation of jugular veins.
1857	Graefe [10]	Venous congestion leading to orbital edema and hypertrophy of fatty tissue	Dilatation of orbital veins on ophthalmoscopic examination; increase of retro-orbital fat found at autopsy.
1857	Egeberg [11]	Degeneration, weakness and elongation of eye muscles	Fatty degeneration and elongation of eye muscles found at autopsy in one case of exophthalmic goiter.
1857	Hervieux [12]	Dilatation and turgescence of orbital arteries	Hyperactivity of heart and marked pulsation of peripheral arteries in exophthalmic goiter.
1860	Aran [13]	Irritation of cervical sympathetic causing contracture of Muller's muscles of orbit	Claude Bernard's demonstration in 1852 that stimulation of the cervical sympathetic in dogs causes exophthalmos; Muller's discovery of smooth muscles in orbit.

TABLE I—*Continued*

Year	Author	Theory of Pathogenesis	Basis for Theory
1864	Laycock [14]	Irritation of cervical sympathetic causing contraction of Muller's muscles of orbit	Claude Bernard's experimental production of exophthalmos by stimulation of first and second dorsal nerve roots; and presence of neuralgic pains along distribution of seventh and eighth cervical and first and second dorsal nerve roots in two cases of exophthalmic goiter observed by Laycock.
1867	Traube and Reckling-hausen [15]	Increase of retrobulbar fat and degeneration of extra-ocular muscles	Autopsy findings in a case of exophthalmic goiter.
1878	Filehne [16]	Brain irritation	Section of restiform bodies in animals resulted in exophthalmos.
1886	Jackson [17]	Brain irritation	Claude Bernard's and Filehne's experimental production of exophthalmos by section of restiform bodies.
1886	Bristow [18]	Increase of orbital fat	Autopsy findings in three fatal cases of exophthalmic goiter.
1894	Buschan [19]	Excessive filling of orbital vessels	Compressibility of bulb; fluctuation of exophthalmos; partial or complete subsidence of exophthalmos after death; pulsation of retinal vessels on ophthalmoscopic examination; sudden appearance of exophthalmos in some patients; production of exophthalmos in rabbits by ligation of jugulars.
1896	Jaboulay [20]	Stimulation of cervical sympathetic	Resection of cervical sympathetic in two cases of Graves' disease was followed by recession of exophthalmos.
1897	Reclus and Faure [21]	Stimulation of cervical sympathetic	For 10 years a patient with marked exophthalmos of Graves' disease could not sleep with closed eyes. Following bilateral resection of cervical sympathetic the exophthalmos receded within 24 hours and the patient was able to sleep with closed eyes.
1900	Edmunds [22]	Hyperthyroidism	Experimental production of exophthalmos in monkeys and rabbits by thyroid feeding.
1907	Landstrom [23]	Stimulation of Landstrom muscle by sympathetic	Rudimentary development of Muller's muscle in man; Landstrom's discovery of smooth muscle between the equator of the bulb and the upper and lower lids.
1907	Birch-Hirschfeld [24]	Stasis of retro-orbital lymphatic vessels	Paraphenyldiamin hydrochloride injections in dogs, rabbits and monkeys produced exophthalmos. Histological studies revealed dilatation of lymph sinuses of orbit.
1912	Fründ [25]	Spasmodic contraction of smooth muscle surrounding ophthalmic veins	Anatomic dissection of the eyes in newborn showed smooth muscle surrounding small and large ophthalmic veins.
1912	Sattler [26]	Brawny edema of retro-orbital tissues	Contraction of Muller's and Landstrom's muscles inadequate to cause exophthalmos. Brawny edema akin to brawny edema met with elsewhere in the body in Graves' disease is most probable cause of exophthalmos.

TABLE I—*Continued*

Year	Author	Theory of Pathogenesis	Basis for Theory
1916	Troell [27]	Orbital edema?	Experiments with paraphenyldiamin hydrochloride in dogs produced orbital edema and exophthalmos even when the cervical sympathetic was extirpated. Stimulation of sympathetic failed to substantiate observations of MacCallum and Cornell and Cannon.
1917	Wilson [28]	Weakness and relaxation of extra-ocular muscles	In eight autopsied cases of exophthalmic goiter very little fat and very little venous engorgement were found. The extra-ocular muscles were small and degenerated. Hence he assumed relaxation of the recti muscles as the cause of the exophthalmos.
1920	Moore [29]	Excess fat, orbital edema and hypertrophy of the extra-ocular muscles	Findings in two cases. Postmortem dissection of the orbit in one case revealed "that after death the exophthalmos was marked and was only as much less than during life as might be accounted for by the draining of blood from the orbit after death. . . . It is clear that in this particular case neither sympathetic irritation nor blood engorgement was the cause of the proptosis. It is difficult to identify what is an excess fat in a cavity which is normally full of it. In this case, however, the orbit was certainly full of it to overflowing with it and nothing else." In the second case exploration of the orbital cavity revealed excess fat. "In addition, however, the fat seemed edematous, and in particular the inferior, internal and external recti muscles were exposed for a considerable distance and these, instead of being thin, flat, ribbon-like muscles, such as one becomes familiar with in squint operations, were greatly swollen fusiform bellies apparently from edematous infiltration, not quite as stout as the joint of one's little finger."
1921	Whitnall [30]	Dilatation of the orbital vessels by excitation of the sympathetic nervous system	"The exophthalmos is said to disappear after death, and in a dissection of two orbits taken from a subject who had died from the disease and had presented the well-marked signs, nothing abnormal could be found by the writer."
1921	Plummer [31]	Dysthyroidism due to action of abnormal thyroxin	In pure hyperthyroidism, clinically encountered in toxic adenomatous goiter, exophthalmos is rarely present. "The characteristics of exophthalmic goiter may be due to an incomplete thyroxin molecule."
1927	Kunde [32]	Hyperthyroidism	Experimental production of exophthalmos in rabbits by administration of thyroid.
1931	Labbe [33]	Thyro-sympathetic hyperactivity	Experimental production of exophthalmos in animals and man by synergetic action of thyroxin and sympathomimetic drugs; recession of exophthalmos under yohimbin therapy.

TABLE I—*Continued*

Year	Author	Theory of Pathogenesis	Basis for Theory
1931	Gasteiger [34]	Localized myxedema of orbital tissues	Observation of one case of postoperative progressive exophthalmos with marked orbital edema and low basal metabolic rate cured by thyroid feeding.
1931	Stewens [35]	Localized myxedema of orbital tissues	Presence of non-pitting edema of orbital tissues in a case of postoperative progressive exophthalmos with low basal metabolic rate. Biopsy of chemotic tissue showed edema and round cell infiltration similar to that found in localized myxedema described by Richter and O'Leary.
1931	Loeb [36]	Hyperpituitarism causing secondary hyperthyroidism	Experimental production of exophthalmos and other signs of Graves' disease by administration of thyrotropic hormone of pituitary to animals.
1932	Crile [37]	Hypothyroidism following operation for hyperthyroidism	Clinical observation of progressive exophthalmos with low basal metabolic rate following operation for hyperthyroidism.
1932–1934	Marine [38, 39, 40]	Hypothalamic stimulation by metabolic disturbances of non-endocrine and endocrine origin	Experimental production of thyroid hyperplasia and exophthalmos by methyl cyanide injections in rabbits; production of exophthalmos by thyrotropic hormone of pituitary; increase of exophthalmos, after thyroidectomy, under continued administration of methyl cyanide and thyrotropic hormone; abolition of exophthalmos by section of cervical sympathetic.
1932–1933	Naffziger [41, 42, 43]	Tremendous hypertrophy of extra-ocular muscles with round cell infiltration of muscles and retro-orbital tissues.	Findings at operation for postoperative progressive exophthalmos with low basal metabolic rate.
1933	Urechia [44]	Thyro-sympathetic hyperactivity	Experimental production of exophthalmos of Graves' disease by injections of thyroxin and ephectonine.
1934	Viallefont and Lafon [45]	Mid-brain irritation	Ocular signs of Graves' disease occur in diseases of the midbrain in the absence of Graves' disease; increase of iodine in midbrain and cerebrospinal fluid in Graves' disease.
1934	Zalka [46]	Inflammatory reaction of orbital tissues	Findings at autopsy in 11 out of 16 cases of Basedow's disease.
1934	Drouet [47]	Primary hyperpituitarism, secondary hyperthyroidism	Clinical and laboratory evidence of hyperactivity of pituitary in Graves' disease; cure of Graves' disease by primary irradiation of pituitary.
1935	Borak [48]	Hyperpituitarism and hyperthyroidism	Cure of cases of Graves' disease including recession of exophthalmos by irradiation of pituitary in patients who were refractory to thyroid radiation.
1936	Thomas and Woods [49]	Chronic inflammatory reaction of orbital tissues	Pathologic findings at operation and autopsy.
1936	Smesler [50]	Inflammatory reaction of orbital tissues secondary to hyperpituitarism	Experimental production of extreme exophthalmos in thyroidectomized and sympathectomized animals by administration of thyrotropic hormone of pituitary; presence of inflammatory reaction in orbital tissues.

of exophthalmos in primary toxic goiter and its great rarity in secondary toxic goiter, is a common observation. In the experience of different observers, the incidence of exophthalmos in primary toxic goiter varies from

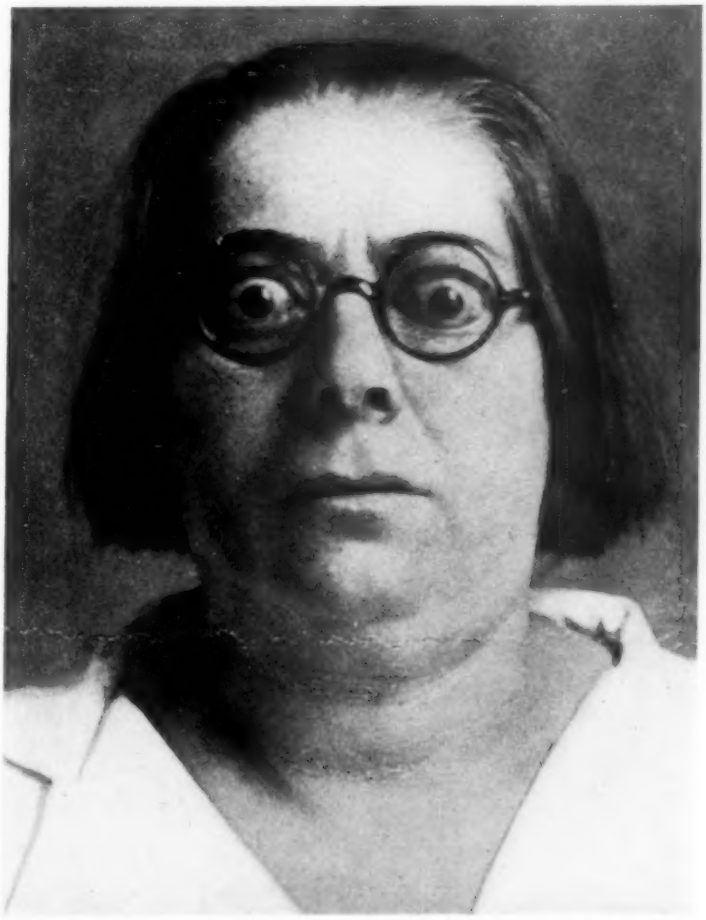

FIG. 1 (Case 1). Postoperative persistent exophthalmos with low basal metabolic rate and myxedema following thyroidectomy and right sympathectomy for Graves' disease. 1925—one year after operation.

50 to 80 per cent, increasing in frequency with the duration of the disease. The degree of protrusion bears no strict relation to the severity of the other clinical manifestations of the disease. Occasionally exophthalmos may be present not only as the first but apparently as the only symptom of Graves' disease. It may then be mistaken for exophthalmos of non-Graves' origin. Its serious import and grave potentiality may then be entirely overlooked, with serious results to the patient. Such an experience at Johns Hopkins Hospital was recently recorded by Friedenwald.[51]

"A patient came to the hospital in 1924 with a history that three months before he had had an acute infection of the upper respiratory tract, rhinitis and fever,

followed a week later by coma and convulsions, which lasted for a week. Three months after the onset he came to the Eye Dispensary, and was found to have moderate exophthalmos of the right eye, with limited movement of the eyeball, a beginning corneal ulcer and the appearance of an orbital abscess. There was no

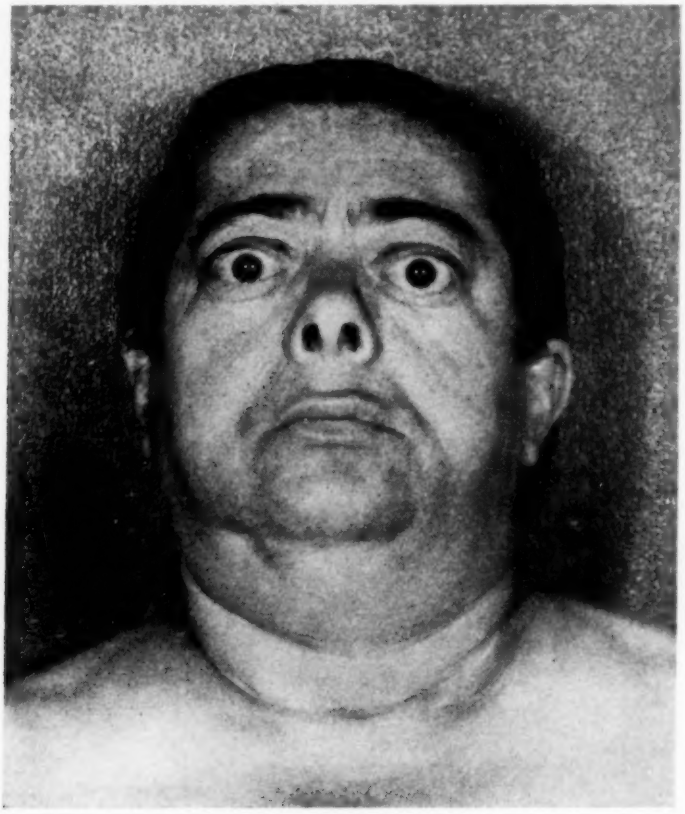

FIG. 2. Same patient as in figure 1. Persistent exophthalmos under thyroid medication. 1932—eight years after operation.

enlargement of the thyroid at that time, and there was no increase in pulse rate. A basal metabolism was not made, but attention was concentrated on the possibility of sinusitis and an orbital abscess. The patient returned three months later, having suffered a great loss of weight. His thyroid was palpable; there was bilateral exophthalmos and papilledema, and the pulse rate was much increased. A diagnosis of acute hyperthyroidism was quite obvious, and the ocular condition was thought to be a possible complication—an abscess of the brain or an orbital abscess. The patient became delirious, bilateral acute glaucoma developed, and he finally died. At autopsy, the orbits were carefully explored on account of the suspicion of an orbital abscess, but no abscess was found, and no note was made of any enlargement. The extra-ocular muscles were preserved, and the specimen was sent to the laboratory. Study showed changes identical with those shown in the cases presented by Dr. Naffziger (table 1)."

2. *Rarity of Serious Eye Complications in the Average Case of Exophthalmic Goiter.* In the mild or average case of exophthalmos in Graves'

disease, no serious eye complications have been encountered. The proptosis may be disfiguring and an annoying symptom but does not constitute a serious clinical problem. As pointed out originally by Stokes and cor-

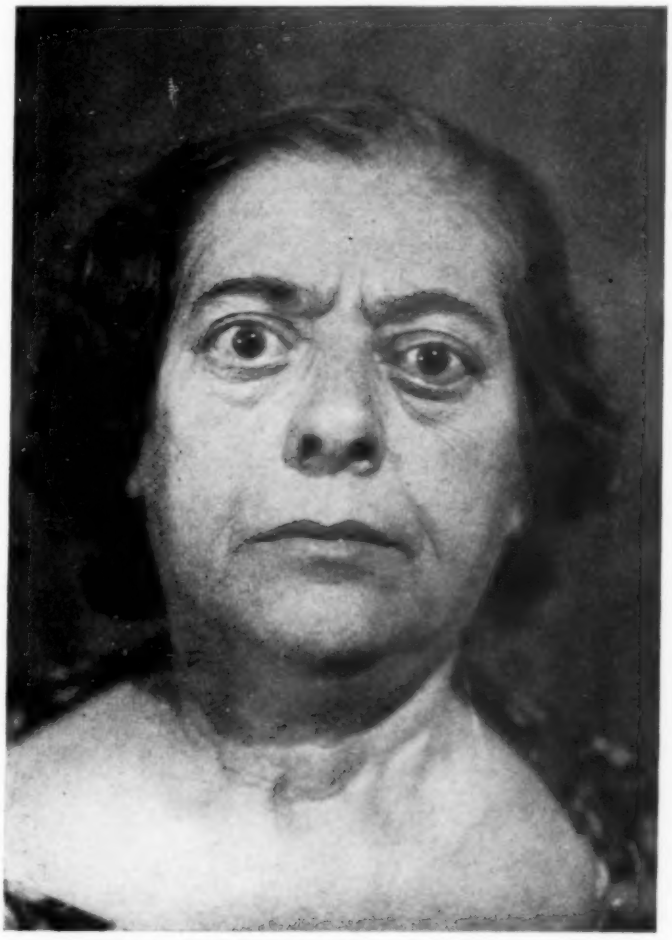

FIG. 3. Same patient as in figure 1. Postoperative persistent exophthalmos with low basal metabolism partially relieved by thyroid medication. 1938—13 years after operation.

roborated by many observers, marked exophthalmos with inability to keep the eyes closed at night may exist for a year or longer without any evidence of conjunctival congestion or impairment of vision. We have observed a patient with postoperative exophthalmos and myxedema over a period of 13 years (figures 1, 2, 3). At times the proptosis was so marked as to result in subluxation of the globes and yet up to now no impairment of vision has been demonstrated on repeated ophthalmological examination. The latest examination made a few months ago showed no contraction of visual or color fields. However, one must not overlook the fact that exophthalmos

in Graves' disease is always a source of potential danger and should always receive prompt medical attention and careful supervision and treatment. One can never tell when an exophthalmos, apparently stationary for many months, may suddenly become progressive and malignant and result in corneal ulceration and destruction of the eye. Such was a recent experience in a patient with exophthalmic goiter whose exophthalmos was stationary

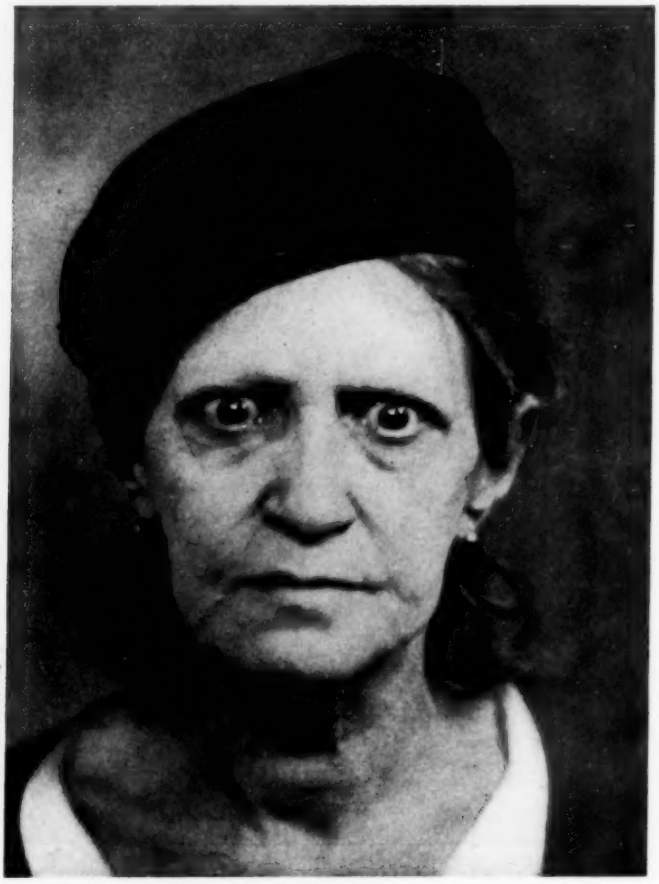

FIG. 4 (Case 2). Marked bilateral exophthalmos in a case of severe Graves' disease. Exophthalmos stationary for a period of eight months.

for many months without any ocular complications. Then, suddenly, after thyroidectomy, within a period of two weeks she developed acute progressive exophthalmos with corneal ulceration and destruction of the left eye which required evisceration (figures 4 and 5).

The danger of delay in the treatment of progressive exophthalmos in Graves' disease was recently stressed by Naffziger in his excellent review of the entire problem: In marked or severe exophthalmos occur muscle palsies, retinitis, optic atrophy, corneal congestion, chemosis, corneal ulcera-

tion, panophthalmitis with loss of both eyes followed at times by meningitis and death.

3. *Recession of Exophthalmos in Graves' Disease after Successful Treatment by Medical or Surgical Measures or Radium and Roentgen Therapy.* In the majority of cases of exophthalmic goiter, following successful treatment by medical, surgical or irradiation therapy, the exoph-

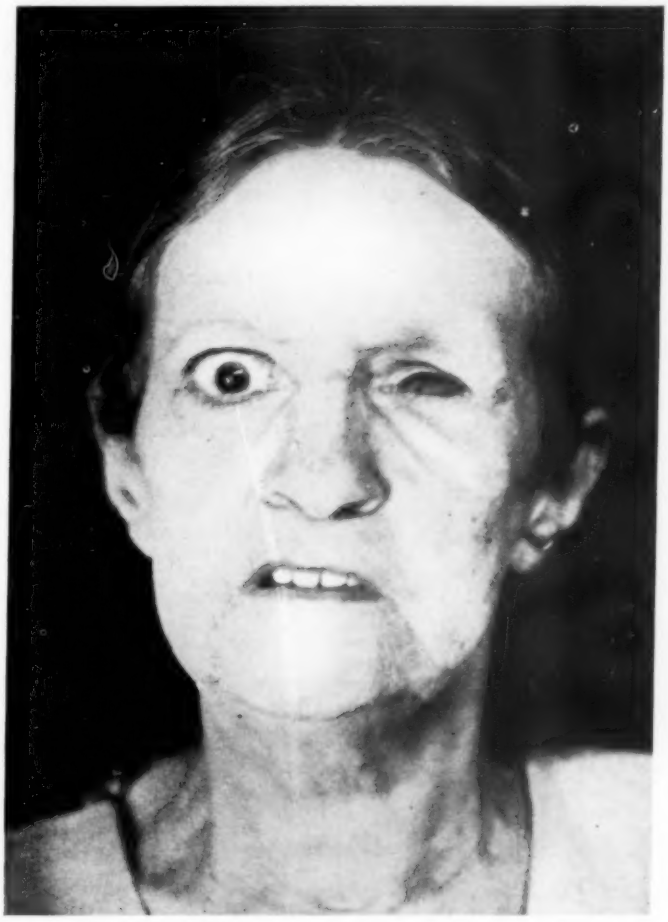

FIG. 5. Same patient as in figure 4. Postoperative progressive exophthalmos with destruction of left eye within a period of two weeks following thyroidectomy and continued use of Lugol's solution.

thalmos recedes completely or partially, or remains stationary, depending upon the duration and the mechanism of production of the proptosis. Evidently one cannot expect the recession of exophthalmos in those long standing cases in which there has taken place marked increase of the retro-orbital cellular tissues with hypertrophy or atrophy and degeneration of the extra-ocular muscles. However, every experienced observer has been im-

pressed by the frequent recession of early exophthalmos when the thyrotoxic symptoms have been controlled and the basal metabolism has been brought down to normal or subnormal rates.

4. *Postoperative Progressive Exophthalmos With Low Basal Metabolic Rate.* Unfortunately, not always does exophthalmos recede after a successful surgical operation for exophthalmic goiter. What is most remarkable—greatly illuminating or puzzling, according to one's theory of the nature of Graves' disease—such cases have been observed after thyroidectomy with sufficient removal of thyroid tissue to produce a normal or minus basal metabolic rate (table 2). In the words of Naffziger, the usual development of the condition is as follows:

TABLE II

Postoperative Progressive Exophthalmos With Low Basal Metabolic Rate

Year	Author	No. of Cases	BMR	Treatment	Result
1925	Plummer [31]	1	−14	Iodine and thyroid.	Improved.
1929	Zimmermann [52]	11	−15 to −19	Iodine and thyroid.	Unimproved.
1929	Benedict [53]	6	Normal	Type of treatment not stated.	"The exophthalmos increased with ecchymosis of the conjunctiva and swelling of the lid and one or both eyes were lost."
1929	Burch [54]	1		Thyroid, iodine, roentgen-ray therapy to orbit.	No improvement. Loss of both eyes.
1930	Roeder and Killins [55]	4	−12 to −21	Thyroid and iodine.	No improvement in any case, aggravation of general symptoms in one case.
1931	King [56]	5	−10 to −19 in 3, normal in 2.	Thyroid and iodine.	Thyroid medication was followed by increase of exophthalmos, iodine gave temporary improvement with relapse.
1931	Earnest and Serger [57]	1	−4	Iodine.	Slight improvement.
1931	Gasteiger [34]	1	Not stated. Myxedematous swelling of eyelids.	Thyroid.	Cured.
1931	Stewens [35]	1	Not stated	Thyroid, roentgen-ray therapy, hypophysin and pituitrin injections.	Thyroid feeding aggravated exophthalmos; roentgen-ray therapy relieved pain but caused no recession; marked improvement after hypophysin and pituitrin injections.
1931	Naffziger [41]	1	−32	Naffziger decompression operation.	Marked improvement.
1932	Naffziger [42]	7	Minus BMR	Naffziger decompression operation.	Marked improvement.
1932	Semmer [58]	1	−13	Naffziger operation.	Marked improvement.

TABLE II—*Continued*

Year	Author	No. of Cases	BMR	Treatment	Result
1933	Merrill and Oakes [59]	2	Minus BMR	Scarification of edematous conjunctiva, multiple punctures, canthoplasty, conjunctivaplasty, resection of redundant welts of conjunctiva, suturing of lids, roentgen-ray therapy to orbit.	No improvement. Corneal ulceration and loss of both eyes.
1934	Cattell [60]	12	Normal	Not stated in 10; Naffziger operation in two.	Not stated.
1934	Bothman [61]	4	−9 to −16 in two; not stated in two.	Iodine, sympathectomy, removal of roof of orbit, Naffziger operation, tarsorrhaphy.	Lugol's solution, bilateral sympathectomy, removal of roof of orbit ineffectual; Naffziger operation gave moderate improvement in one; tarsorrhaphy in another.
1934	Goldenberg [62]	1	−17.8	Canthotomy, later. Naffziger operation.	Improvement after Naffziger operation.
1934	Nordland and Larsen [63]	2	−19 and −32	Not stated.	Progressive exophthalmos.
1934	Brisay [64]	3	plus 8 to minus 23	Iodine, thyroid, eserine salicylate, ergotamine tartrate, excision of a piece of conjunctival sac, tarsorrhaphy.	Improvement in two cases; result not stated in one case.
1936	Rynearson [65]	2	−4 to −14	Iodine and thyroid.	Improved and relapsed despite prolonged treatment in one case; result "to be noted in the other."
1936	Thomas and Woods [49]	14	Normal in 12; myxedema in two with BMR −30 in one and plus 35 in the other.	Thyroid in five cases; iodine in two; tarsorrhaphy in three; roentgen-ray therapy to orbit in one.	No improvement. No improvement. Not stated. Improved.
1937	Rudemann [66]	4	Not stated, myxedema of orbit present.	Roentgen-ray therapy.	"In none of them is the exophthalmos progressing as before."

"Thyroidectomy is performed on a patient with exophthalmic goiter who presents the usual elevated basal metabolic rate and cardiovascular and nervous manifestations. Clinical improvement follows, except that the exophthalmos does not disappear. In a variable period, often in three or four months, it becomes evident that the proptosis is increasing. As it proceeds an increased fullness of the lids is noted; then lacrimation and epiphora appear. A watery appearance of the scleral conjunctiva is followed first by edema near the inner canthus and then by swelling, which spreads rapidly, and protrusion of the inferior palpebral mucosa. Diplopia and lack of parallelism of the eyes are followed by an increasing limitation of the movements of the globe, and downward movements are the only ones retained ultimately. In other directions there may be only slight movement. During the increasing protrusion of the eyes through these stages the lids no longer completely cover the globe, and the cornea

becomes exposed. Such patients are said to be suffering from malignant exophthalmos, for while cases of less severity may be seen, the severe cases invariably have progressed to the stage of corneal ulceration and infection. Many enucleations have been performed, but the usual termination has been an infected orbit, intracranial extension of the infection and death."

5. *Treatment of Postoperative Progressive Exophthalmos With Low Basal Metabolic Rate.* The treatment of severe cases of postoperative progressive exophthalmos with low basal metabolic rate by the usual methods of sympathectomy, tarsorrhaphy, canthotomy, corneal scarification and local eye applications have not been satisfactory (table 2). In many of these cases, despite such treatment, ulceration of the cornea and destruction of the eyes could not be averted. In some, even if the eyes were saved, marked impairment of vision from keratitis, retinitis, or optic atrophy, resulted. The dread and hopelessness with which this condition was looked upon by the profession can best be visualized by citing the following quotation from a recent publication of an experienced thyroid surgeon.

"A man, aged 36, consulted me in 1928, with an acute and very active exophthalmic goiter. He was operated upon, made an excellent recovery, gained weight, and felt fine for a period of four months, when his father became ill and he was called East to be with him through a long and distressing illness, resulting in death. My patient returned to Seattle in April, 1930, with evidence of recurrence of his goiter. In addition to the usual symptoms of moderate severity, he then had a slight degree of bilateral exophthalmos. He was reoperated on in the latter part of April, again making a good recovery. All symptoms of goiter, except exophthalmos, soon disappeared. The condition of his eyes rapidly became worse—the prominence accentuated, the edema more pronounced, the difficulty with vision increased to a point at which he is unable to work. Twice during recent months, the vessels surrounding the cornea have become injected similar to the condition seen in association with corneal ulcer though no ulcer has as yet developed. I feel that if an ulcer develops in this man's cornea, the probability of blindness following it is very great. . . . As yet no satisfactory treatment has been devised for this most distressing condition."

Hardly had Dr. King pronounced this gloomy prognostication when one of the most dramatic announcements—with which medical history is so replete—was made by Dr. Naffziger of San Francisco, who attended the meeting at which Dr. King read his paper on "The Cause of Exophthalmos" in Graves' disease.

"A nurse," Dr. Naffziger began, "had, following thyroidectomy, a rapidly increasing exophthalmos with a low (minus 32) basal metabolic rate. Her vision had become so impaired that she could not recognize people at five feet. This was due to a papillitis associated from some atrophy. In view of her desperate condition, it seemed justifiable to explore the orbit and decompress it. This was done through a frontal flap exposing the orbit from above. The orbital plate was then removed on the right side. The contents appeared very tense and bulged through the decompression. The tissues appeared somewhat edematous. The fat did not appear to be increased, nor was it under tension. The cone of extra-ocular muscles was tense, but the striking feature was their great thickness. The muscle fibers were separated in the line of their direction. They did not cut like normal musculature. The question then arose as to why the choked disc existed. It appeared possible that

the nerve might be compressed at the foramen. The optic nerve was exposed through the musculature and appeared normal. In order to free the optic nerve posteriorly bone was removed from the optic foramen and the ring of Zinn was opened, actually decompressing the optic nerve itself. Following operation, there was reduction by the exophthalmometer from 34 to 23, which subsequently came up to 27, but never exceeded that level. From the fifth day the vision was markedly improved. The patient was able to read with that eye shortly after. She was so pleased with the result that about three weeks later she returned with a request that the other eye be operated upon. This was done with the same pathological findings and with the same results. The microscopic picture of the muscle is one of marked fibrosis, round cell infiltration and hyaline changes."

One year later Naffziger was able to report on five more patients in whom the clinical course and operative findings paralleled those of his first case. The results of the decompression operation were uniformly successful.

"In each instance there was early improvement in vision, subsidence of the papillitis and disappearance of the hemorrhage. The recession of the globes continued over many months and varied from 2 to 7 degrees on the exophthalmometer. In no case has there been any tendency to recurrence. In each instance the globes show faint pulsation of which the patient is unaware."

Medical Treatment of Postoperative Progressive Exophthalmos with Low Basal Metabolic Rate

While the beneficial results of the Naffziger operation have been confirmed by a few other surgeons, the operation is a formidable one. The amount of recession of the exophthalmos is only moderate in degree. Although the pulsation of the globe in the cases personally operated upon by Dr. Naffziger has been only faint, we have been informed of one case done by a neuro-surgeon where the pulsation was sufficiently marked to make the patient disagreeably conscious of its presence. Moreover, the rationale of the procedure is mechanical relief: the Naffziger decompression operation does not remove the underlying basic cause of the pathologic process. Hence in the milder grades and in the earlier stages of progressive exophthalmos medical treatment has its place and has been carried out by a number of clinicians.

The first to report on the successful medical treatment of a case of postoperative progressive exophthalmos with low basal metabolic rate was Dr. Henry S. Plummer from the Mayo Clinic in 1925. Before operation for exophthalmic goiter the patient had shown a basal metabolic rate above plus 80

"and since operation a rate of −14, characteristic nervous phenomena and progressive exophthalmos. When this patient is placed on Lugol's solution, the nervous phenomena disappear, the exophthalmos recedes, the basal metabolism drops to −28, and edema, slow speech, and so forth, the characteristics of myxedema, appear within two weeks. When iodine is administered and the basal metabolism is maintained at the average normal with thyroxin, there is no evidence of disease except slight

exophthalmos. Many similar cases have been observed. . . . I have seen the complex that terminates in panophthalmitis and loss of the eyes progress rapidly almost to the point of forcing enucleation, stop and begin to recede within five hours after 100 minims of Lugol's solution had been given."

Unfortunately, Plummer's favorable results in postoperative progressive exophthalmos with low basal metabolic rate by means of iodine and thyroid treatment were very rarely obtained by other observers (table 2). Thus in 11 cases reported by Zimmermann no benefit was obtained from the combined use of iodine and thyroid. In one case, reported by Burch, iodine and thyroid failed to produce any improvement and the patient lost both eyes. In four cases observed by Roeder and Killian, thyroid and iodine produced improvement in no case and aggravation of symptoms in one. In King's five patients iodine medication gave temporary improvement with relapse, while administration of thyroid was followed by increase of exophthalmos. A cure in one case was reported by Gasteiger, but his patient presented frank myxedema of the orbits. Stewens, Naffziger, Semer, Merrill and Oakes, Cattell, Bothman, Rynearson, Thomas and Woods failed to obtain any benefit from iodine and thyroid medication. Favorable results in one case were claimed by Stewens from the use of hypophysin and pituitrin injections and in two cases by Brisay from the combined use of iodine, thyroid, eserine salicylate, ergotamine tartrate plus excision of a portion of the conjunctival sac and tarsorrhaphy. In short, with few exceptions, medical therapy has been rather disappointing in severe forms of postoperative progressive exophthalmos with low basal metabolic rate.

Radiotherapy to Orbital and Pituitary Regions in Postoperative Progressive Exophthalmos with Low Basal Metabolic Rate

The first to mention the use of roentgen therapy for the treatment of postoperative progressive exophthalmos was Burch in 1929. After iodine and thyroid had failed to produce any benefit the malignant clinical course of the exophthalmos suggested the diagnosis of sarcoma of the orbit. Intensive irradiation was used. There was no improvement and the patient lost both eyes from corneal ulceration and destruction. Burch gives no details as to the technic of the roentgen-ray therapy used in his case. In view of the diagnosis of sarcoma of the orbit, it is fair to assume that very large doses of roentgen-rays were used, with probable deleterious result. While large doses of roentgen-rays are frequently helpful, at least temporarily, in malignant growths, they are usually harmful in inflammatory and degenerative processes. Hence the failure of roentgen-ray therapy in this case is no criterion of the value of proper irradiation of the orbit in postoperative progressive exophthalmos, in which condition the most constant pathologic findings are those of inflammation of the orbital cellular tissues and hypertrophy or atrophy and degeneration of the extra-ocular muscles. In the next case, reported by Stewens in 1931, pain in the eye was relieved promptly but recession of exophthalmos was not obtained after

the use of a small dose of roentgen therapy. Nor were Merrill and Oakes more fortunate in their results. Definite improvement from orbital irradiation was first reported by Thomas and Woods in 1936 in one case and by Rudemann in 1937 in four cases. In a case recently observed in the Out-Patient Department of Beth Israel Hospital, the prolonged use of iodine and thyroid was a complete failure while roentgen-ray therapy to the orbital and pituitary regions was of distinct benefit.

Case Report

In the early part of October 1935, without any apparent predisposing or exciting causes, M. E., aged 51 years, became nervous, irritable and shaky. Not until six months later did he notice slight protrusion of his eyes. Although he retained his strength and was able to carry on his usual work as pressor of cloaks, the staring and terror-stricken expression of his eyes and his trembling hands made his employer regard him distrustfully and make disparaging remarks about his "crazy" looks and

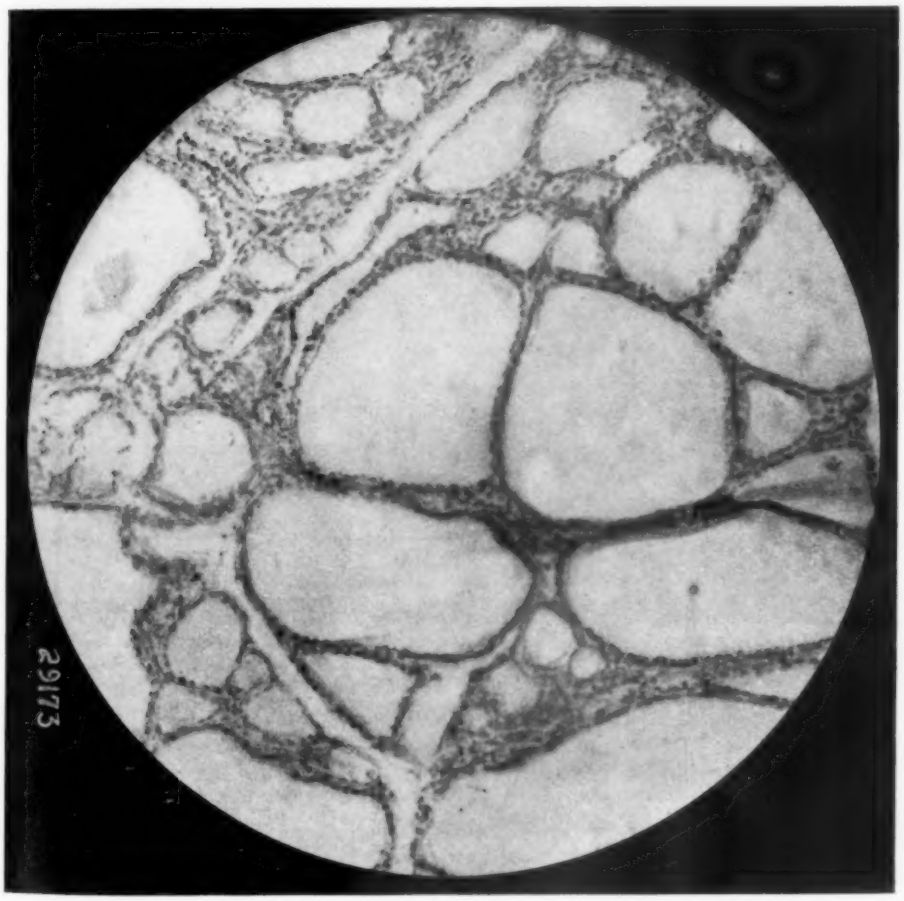

Fig. 6 (Case 3). Microphotograph showing moderate thyroid involution following the preoperative use of 360 minims of Lugol's solution.

shaking hands. Humiliated and unnerved by these remarks, he left this place to look for employment in a more friendly environment. He was successful in this quest, but the change failed to produce any improvement in his condition. His irritability and nervousness grew more marked. He had unaccountable and uncontrollable outbursts of temper which greatly distressed and puzzled him. It was for this change in temperament that he first consulted a physician in May 1936, seven months after the onset of his first complaints.

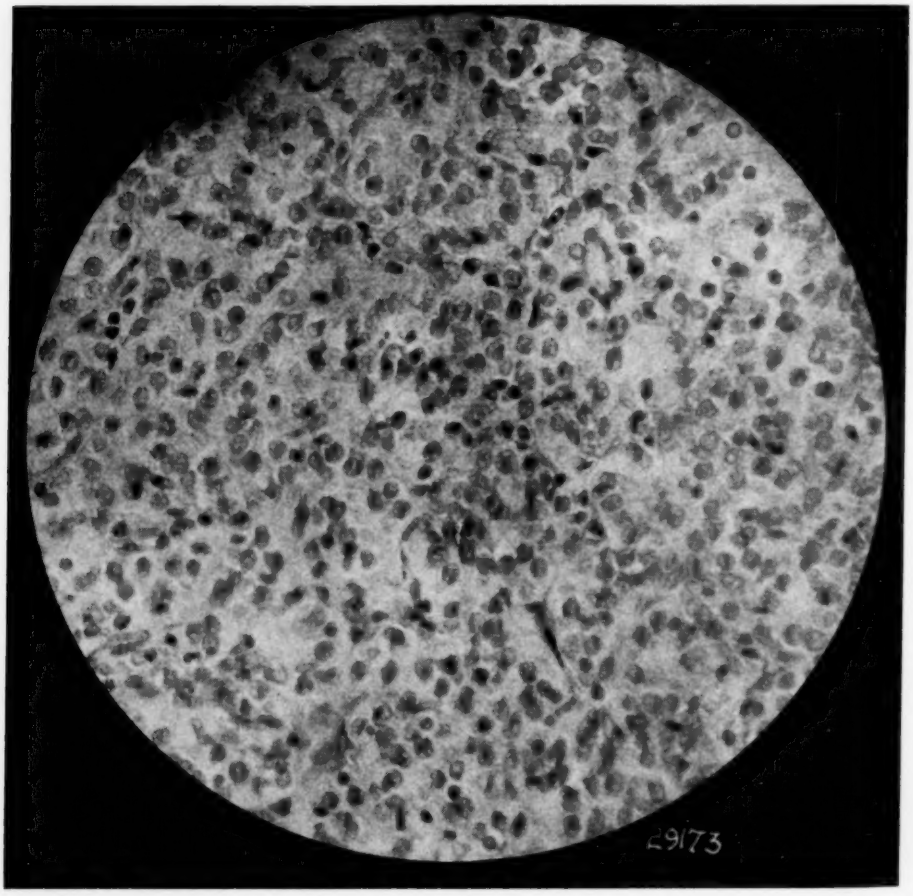

FIG. 7. Marked thyroid hyperplasia and hypertrophy. Microphotograph of a different field from same section of excised thyroid in case 3. Compare with figures 6, 8 and 9.

The examination failed to elicit any thyroid enlargement, but the other signs of exophthalmic goiter were unmistakable and a basal metabolism was suggested. He refused to take the test because he "still felt too well" to undergo a special examination for which a fee had to be paid. He was given sedative medication but his irritability and emotional outbursts gradually increased. He lost weight and strength progressively. The exophthalmos became more marked. Strangely enough, despite all the classical signs of Graves' disease, he had no heat intolerance but the reverse. During the months of July and August he frequently felt chilly and his hands would get blanched and "dead-like."

Towards the end of August 1936, his general condition had greatly deteriorated and his loss of weight amounted to 20 pounds. He felt very weak and shaky and was forced to give up his work. He felt greatly depressed and cried frequently under slight or no provocation.

In September, 1936, he was admitted to the Surgical Service of Beth Israel Hospital. On examination he showed all the classical signs of exophthalmic goiter

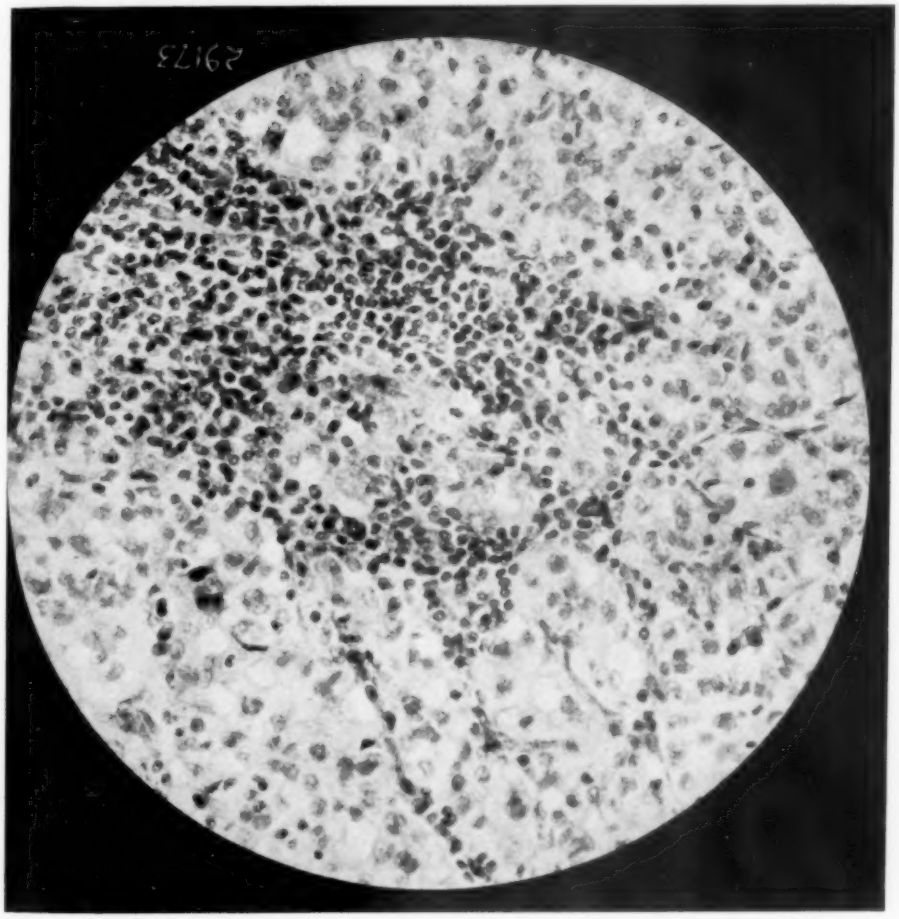

FIG. 8. Marked thyroid hyperplasia, hypertrophy and round cell infiltration. Microphotograph of another field from the same section of excised thyroid in case 3. Compare with figures 6, 7 and 9.

with marked exophthalmos and slight thyroid enlargement. The basal metabolism was plus 25. Physical and radiographic examination of the heart and lungs was negative. Blood and urine analyses were practically normal.

A diagnosis of uncomplicated exophthalmic goiter was made and thyroidectomy decided upon.

Following the use of 360 minims of Lugol's solution over a period of 15 days, the basal metabolism dropped to plus 12 and on October 10, 1936, a subtotal thyroidectomy was performed under general anesthesia by Dr. I. Busch. A study of the

excised thyroid tissue revealed marked iodine involution of the greater part of the microscopic field with many discrete areas of persistent glandular hypertrophy and hyperplasia, round cell infiltration and lymphoid hyperplasia (figures 6, 7, 8, 9).

The postoperative course was uneventful but the use of Lugol's solution was continued 5 minims three times daily. On October 21, 1936, 11 days after operation, the wound was healed, the patient's general condition was greatly improved and

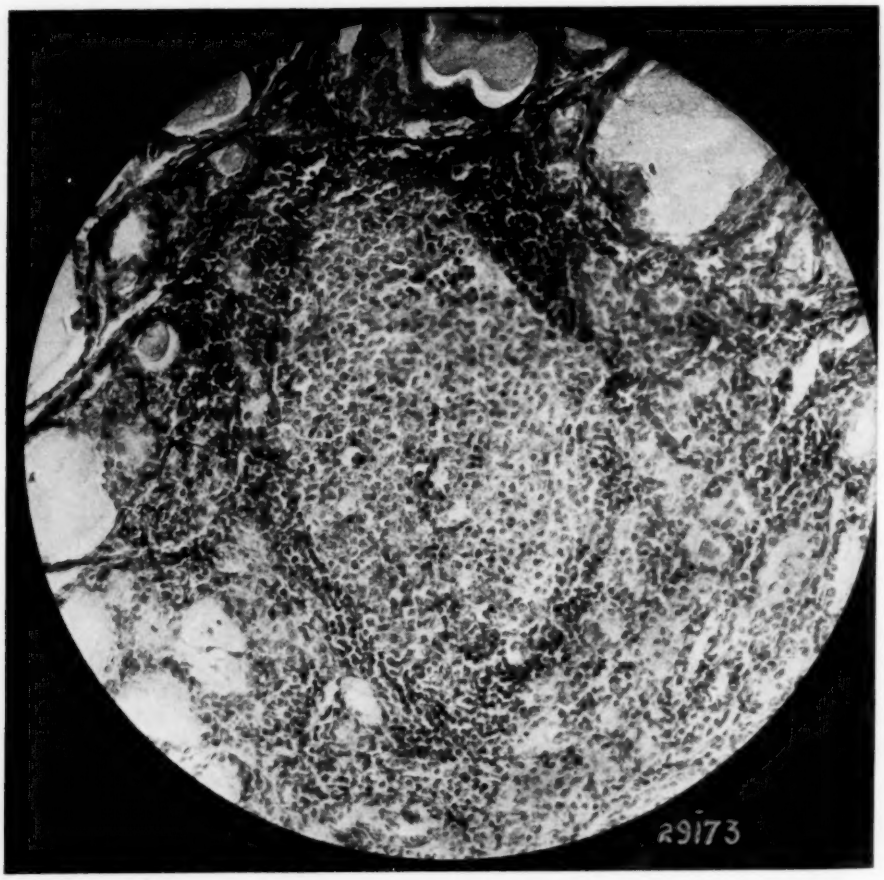

FIG. 9. Moderate thyroid hypertrophy and marked lymphoid hyperplasia. Microphotograph of another field from the same section of excised thyroid in case 3. Compare with figures 6, 7 and 8.

the basal metabolism had dropped to minus 11. He was discharged from the hospital and was advised to continue the use of Lugol's solution. Nevertheless, despite the continued use of iodine the exophthalmos did not recede, and one week later was definitely on the increase. He was then promptly referred for treatment to the out-patient eye clinic. On November 15, 1936, he was examined by Dr. Slomka of the ophthalmological department who found bilateral exophthalmos and all other ocular signs of Graves' disease. There was no lagophthalmos. The lids closed completely. The conjunctivae were congested but the media were clear. The fundi showed slightly pale optic discs. The retinal vessels were thin but otherwise normal.

Under continued use of Lugol's solution and local eye treatment there was no improvement. On November 30, 1936, the exophthalmos had noticeably increased. The protrusion of the left eye was 22 mm., that of the right 27 mm. The right conjunctiva was congested. The cornea and media were clear. The left fundus showed

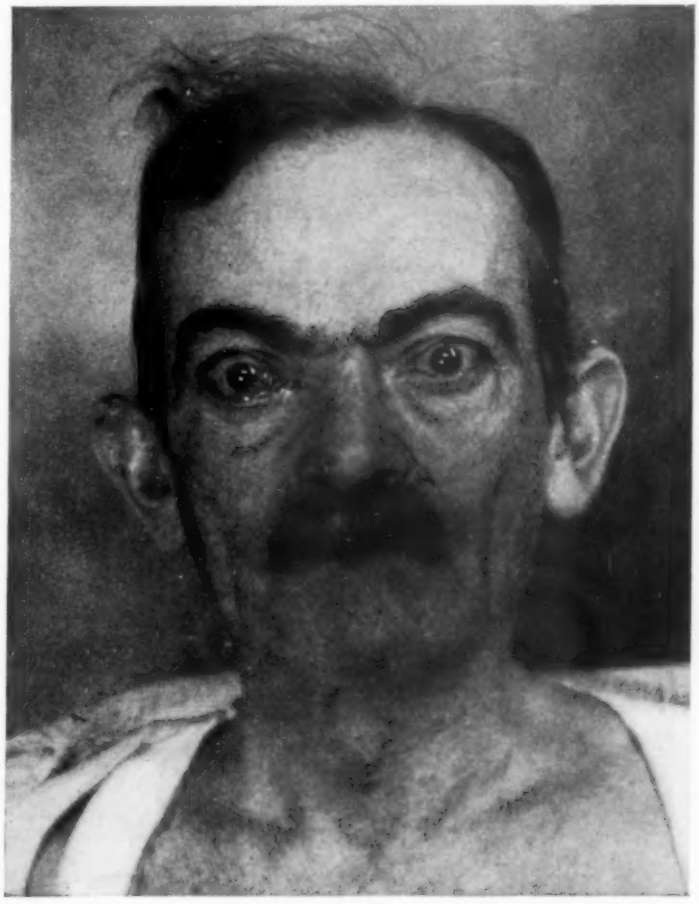

FIG. 10 (Case 3). Postoperative progressive exophthalmos with low basal metabolic rate three months after operation and continued use of Lugol's solution.

no abnormality, the right showed slight venous congestion. For the next six weeks, despite the continued use of Lugol's solution and local eye medication, the eyes failed to improve (figure 10). A basal metabolism test on January 19, 1937, showed 18 per cent minus. He was then placed on desiccated thyroid grain 1 three times daily, increased later to grains 2 three times daily. There was no improvement. On April 20, 1937, the basal metabolism had risen to plus 13. His pulse showed moderate acceleration and he had slight tremor of fingers but the eyes were much worse. Exophthalmometric readings showed protrusion of the left 22.5 mm., that of the right 30 mm. The right conjunctiva was markedly congested and chemotic. The fundi were normal and there was no contraction of the visual fields.

For the next three weeks local treatment of the eye and the internal use of Lugol's

solution and desiccated thyroid were continued without any improvement. At this time the chemosis and congestion of the right conjunctiva were very marked and diplopia developed due to paresis of the superior and external right rectus muscles (figure 11). The marked progression of the exophthalmos in the right eye and the apparently stationary condition in the left raised the question of a possible orbital

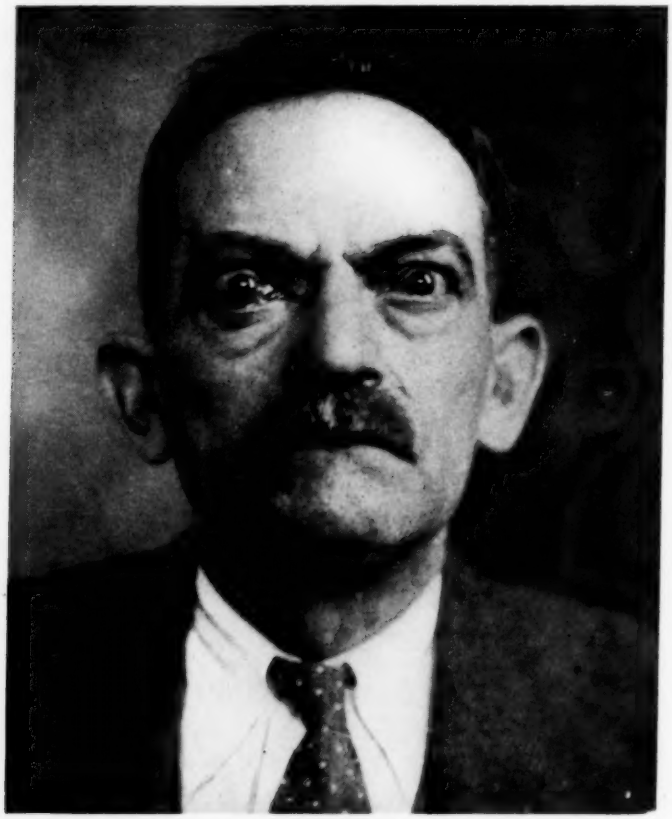

FIG. 11. Same case as in figure 10, showing progression of exophthalmos despite prolonged use of iodine and thyroid (May 24, 1937).

neoplasm and a roentgen-ray study of the orbit was made. The radiologist's report on May 12, 1937, stated: "The cranial cavity is of normal size. The cranial vault is of normal thickness. There is no increase in intracranial pressure. There is no abnormal intracranial calcification. The sella turcica is normal in size, shape and position and shows no lesion or destruction. There is no calcification of the petro-clinoid ligament or inter-clinoid ligament. The frontal sinus on the right side is rudimentary."

The advisability of a Naffziger orbital decompression operation was considered, but the formidable nature of the operation made us decide to try orbital and pituitary irradiation first in the belief that the pathogenesis of progressive exophthalmos in Graves' disease is most frequently, if not invariably, dependent upon a local inflammatory condition of the orbital tissues. The patient was therefore referred to the Radiation Therapy Department, Dr. I. Seth Hirsch, Director. Following a series

of five roentgen-ray treatments, 500 *r* of heavily filtered high voltage roentgen-rays. to each pituitary-orbital region, given between May 12 and June 6, 1937, improvement was noted (figure 12). The treatments were therefore continued and an additional dose of 500 *r* was given to each region. On July 7, 1937, a day after the series of roentgen treatments was completed, the protrusion of the right eye was

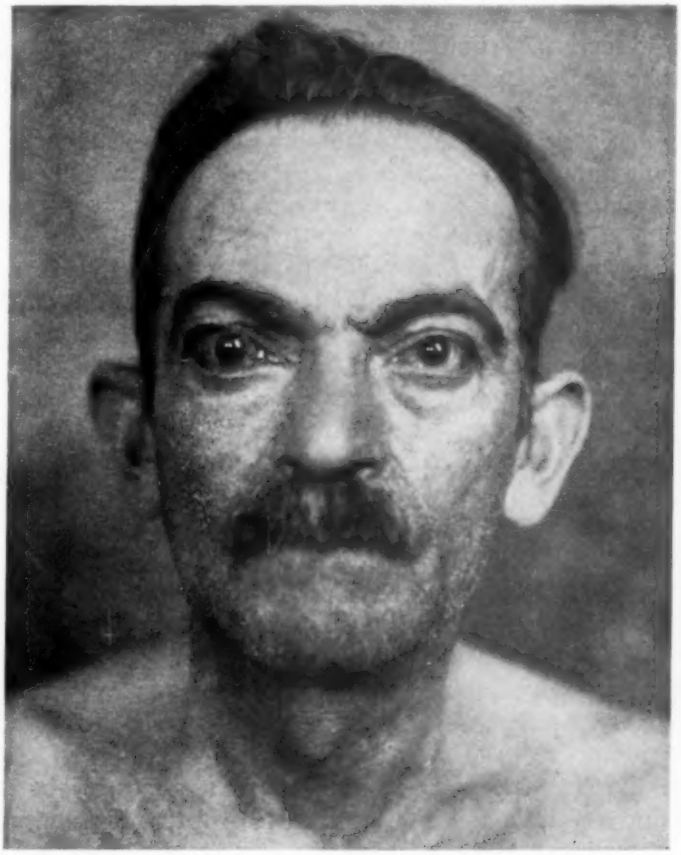

FIG. 12. Regression of exophthalmos following roentgen therapy to orbital and pituitary regions (June 18, 1937).

reduced from 30 to 29 mm., the conjunctival congestion was less marked and, subjectively, the patient felt greatly relieved. The improvement continued, the chemosis of the right conjunctiva lessened, the diplopia diminished and in September he felt sufficiently comfortable to resume his occupation, at which he has worked regularly ever since. In October the diplopia was present only occasionally. In November the conjunctival congestion was almost entirely gone and the diplopia was negligible and rarely present. His general health was good and he showed no evidence of thyroid disturbance. The exophthalmos showed further regression—right eye 27 mm., left 22 mm.—and the extra-ocular palsies were less marked.

Comment

The important points deserving emphasis in this case are:

1. The striking change in temperament as the main clinical manifestation of Graves' disease for nearly six months before the appearance of exophthalmos or other signs of the disease.

2. The absence of clinically perceptible thyroid enlargement in the presence of marked exophthalmos eight months after the onset of Graves' disease.

3. The presence of marked exophthalmos and other symptoms of thyrotoxicosis with comparatively low basal metabolism at the height of the disease. The highest basal metabolic rate before the preoperative use of Lugol's solution was only plus 25.

4. The presence of the histological pathology of active Graves' disease in the excised thyroid tissue. Despite the abundant preoperative administration of Lugol's solution (360 minims) over a period of 15 days, which brought the basal metabolism down to plus 12, the excised thyroid tissue still showed many areas of hypertrophy, hyperplasia, round cell infiltration and lymphoid hyperplasia—the characteristic histopathology of active Graves' disease. These microscopic findings unmistakably warn us that the preoperative use of iodine does not completely abate the pathologic change in the diseased thyroid gland in Graves' disease. Hence subtotal thyroidectomy in diffuse toxic, or exophthalmic, goiter does not remove all the diseased thyroid tissue. Although the surgeon may remove sufficient thyroid tissue to reduce the basal metabolism to a minus rate, the remaining pathologic tissue in the thyroid may continue to secrete an abnormal thyroid product or liberate an unknown noxious agent which may affect selectively various organs and tissues, among which the orbit has been a common site.

5. The development of progressive exophthalmos, right much more marked than left, three weeks after a successful thyroidectomy which produced marked general improvement and a drop in basal metabolism to minus 11.

6. The failure of the prolonged use of iodine and thyroid medication to control postoperative progressive exophthalmos with low basal metabolic rate. Following the use of Lugol's solution the basal metabolism dropped from minus 11 to minus 18 but the exophthalmos failed to recede. When, in addition, desiccated thyroid was given over a period of several months the basal metabolism rose from minus 18 to plus 13 with development of symptoms of hyperthyroidism and aggravation of the exophthalmos.

7. The favorable results obtained by roentgen-ray treatment directed to the orbital and pituitary regions. While no definite conclusion can be drawn from the treatment of this case alone, the equally encouraging results reported by Thomas and Woods of Johns Hopkins Hospital and Rudemann

of the Crile Clinic, make early roentgen-ray therapy to the orbital and pituitary regions a method deserving a further trial in the treatment of exophthalmos of Graves' disease whenever it becomes a clinical problem.

Summary and Conclusion

More than a century and a half after Parry first described exophthalmic goiter, the basic cause of the disease remains entirely unknown and a specific form of treatment has not been discovered.

Until such time as a specific method of treatment shall be discovered, we have to depend upon empirical methods of treatment—medical, radiotherapeutic or surgical.

Graves' disease, or exophthalmic goiter, is not synonymous with hyperthyroidism. Although it is usually accompanied by an elevated basal metabolism, it may also manifest itself with a normal, low or minus basal metabolic rate. Indeed, Graves' disease and myxedema may be associated at the same time. The most significant and distinctive striking feature of Graves' disease—*exophthalmos*—may be present not only with an elevated metabolism but also with a minus basal metabolic rate. Some of the worst forms of progressive exophthalmos with corneal ulceration and loss of both eyes have been observed in patients after successful thyroidectomy with control of general symptoms and a drop in basal metabolism to a minus rate.

In the vast majority of cases investigated pathologically, progressive exophthalmos in Graves' disease is not a purely functional condition induced by hyperthyroidism or hypothyroidism or a fanciful mutually-exclusive combination of hyperthyroidism-hypothyroidism. Although in some cases of postoperative progressive exophthalmos with low basal metabolic rate the combined use of iodine and thyroid medication produced a regression of the lesion, it failed to do so in the vast majority of reported cases, as it likewise failed in our own case.

The most frequent pathologic findings in progressive exophthalmos—preoperative or postoperative—have been those of an inflammatory condition of the orbital cellular tissues and hypertrophy or atrophy and degeneration of the extra-ocular muscles.

Until the introduction of the Naffziger decompression operation the usual medical and surgical methods had failed to cope successfully with the severe forms of postoperative progressive exophthalmos with low basal metabolic rate.

The favorable results of roentgen-ray treatment of the orbital and pituitary regions in cases of postoperative progressive exophthalmos with low basal metabolic rate suggest the early use of radiation therapy in combination with medical treatment for exophthalmos in Graves' disease whenever it becomes a distinct clinical problem. Only if adequate radiation therapy fails, should the Naffziger operation be considered in severe progressive exophthalmos.

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THE OCCURRENCE AND CLINICAL SIGNIFICANCE OF HEMOCONCENTRATION *

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Several years ago attention was called (Moon), to changes in blood concentration incident to shock. The accumulation of additional data, from clinical and experimental sources, justifies further consideration of this subject. The term *hemoconcentration* will be used to designate a rapid increase in the erythrocytic content of the blood. Some authors have shown concentration by increased specific gravity of the blood, and have given no data concerning the red cells. The specific gravity of red cells is higher than that of plasma, hence erythrocytosis raises the specific gravity of the whole blood. In order to include such observations in the discussion, the term hemoconcentration rather than acute erythrocytosis has been chosen.

Hemoconcentration is demonstrable either by hematocrit readings, by an elevated specific gravity of the whole blood, by an increased hemoglobin content or by an increased erythrocytic count. Before the development of laboratory methods, observers occasionally recorded that the blood was thick, dark and slow to clot. The conditions in which this observation was made were of the same type as those in which hemoconcentration has been demonstrated by laboratory methods in later times.

A *persistent* erythrocytosis occurs in certain forms of chronic cardiac deficiency, in emphysema, in those who live in high altitudes, in chronic carbon monoxide poisoning and in primary polycythemia, otherwise known as polycythemia vera. Those interested in these conditions will find them discussed in a monograph by Weber and in a review by Harrop.

In contrast to the conditions mentioned, a rapid marked increase in the erythrocytic count is a frequent event in acute illness of diverse kinds. This phenomenon has been imperfectly understood. Its occurrence and significance are not discussed in treatises on clinical medicine nor in the literature of hematology. Since no review on this subject has been published, it seems appropriate to assemble such observations as have been found and to consider their significance. Observations on hemoconcentration occur occasionally in clinical reports, and the titles of the articles give no indication of this feature. Hence the data presented here can not represent a complete review of the subject.

Hunter (1890) observed that the injection of a large amount of blood into the peritoneal cavity of animals was followed by a rapid increase in the specific gravity of the blood. This increase amounted to 40 per cent within three hours and " was accompanied by a condition closely resembling shock." He attributed the high specific gravity not to the absorption of the injected

* Received for publication September 12, 1938.

corpuscles, but to the escape of fluid from the blood. Sherrington and Copeman (1893) made an extensive study of the specific gravity of the blood under various experimental conditions. They recorded that in shock, induced by obstructing the circulation or by opening the abdomen and manipulating the viscera, the specific gravity of the blood was markedly increased. Conversely, the specific gravity declined progressively after hemorrhage (repeated withdrawals of blood by venepuncture).

Cobbett (1897) described a series of experiments in which the specific gravity of the blood was compared with arterial blood pressures after manipulation of the intestines of dogs. For a time the specific gravity was unchanged, but as edema and serous effusions developed, the specific gravity rose steadily and the blood became thickened so that it flowed with difficulty. For some hours after the specific gravity began to rise, the arterial pressure showed little or no sign of falling. When at last the blood pressure began to decline, it fell rapidly and death occurred soon. He noted that circulatory failure after abdominal operations, in peritonitis and after burns, is accompanied by similar alterations in the blood.

King (1902) noted an increase in red blood cells after surgical operations in a series of cases. He was puzzled by the fact that this occurred even when considerable blood had been lost incident to the operation. One case, which died in shock 36 hours after operation, had a numerical increase of 2,100,000 red blood cells. The increase was much less in non-fatal cases. He attributed the hemoconcentration to loss of fluid from the blood.

Vale (1904) recorded the specific gravity of the blood and tissues in experimental shock in animals and in human cases of shock from various causes. In experimental shock the specific gravity was increased and that of the tissues decreased, indicating an increased fluid content of the tissues and a consequent inspissation of the blood. Shock in human cases, resulting from trauma, burns, peritoneal inflammation and from other causes, was accompanied by an increased specific gravity of the blood. This returned to normal when recovery from shock occurred. Vale believed that the phenomena resulted from damage to capillary walls. He was the first author to suggest that variations in specific gravity of the blood present a practical means for distinguishing between shock and hemorrhage.

Crile (1909) recorded that in experimental shock the red cells are increased in number but after hemorrhage their number per unit volume is decreased. Henderson (1910) found the blood abnormally concentrated in shock and attributed it to the passage of serum out of the vessels into the tissues. Mann (1914) reported an increase in the specific gravity of the blood in shock.

During the World War intensive studies were made on shock, its nature and conditions of occurrence. Cannon, Fraser and Hooper made examinations of the blood which confirmed the observations previously cited. They found red cell counts ranging from 6,000,000 in mild shock to above 9,000,000 in severe shock. The hemoconcentration was progressive and

tended to be proportional to the degree of shock. Conversely, a decreased number of erythrocytes was found after hemorrhage and also in the blood of those who had served as donors for transfusions. Bayliss and Cannon found corresponding hemoconcentration in experimental shock in cats. M. C. Bazett found red cell counts of great value as indicating whether shock or hemorrhage was present, and in determining the condition of the patient and the operative risk. In Robertson's experience patients suffering from shock are to be distinguished from cases of hemorrhage, or from hemorrhage plus shock, by the presence of a high hemoglobin reading in the former.

These findings were confirmed by Keith who showed that a marked decrease in the total volume of blood is an outstanding feature of shock. This was due to a decrease in the plasma volume and was accompanied by hemoconcentration. He emphasized that in shock the normal processes of blood dilution fail to operate. In moderate shock the blood cannot absorb fluid from the tissues nor from the gastrointestinal tract, but the vascular walls are able to retain fluid if supplied in suitable form. In severe shock the vascular walls are unable to retain colloids or even whole blood. Fluids leak out into the tissues almost as fast as injected. Treatment in this class of cases was entirely ineffective.

Bainbridge and Bullen found the hemoglobin content reduced after hemorrhage and increased during shock. They advised this as a practical means for the differentiation of those conditions. They observed that the system is able to compensate for loss of blood by hemorrhage but that in shock this mechanism failed to operate. The mechanism of compensation is discussed in a subsequent section.

Erlanger, Gasser and their associates retarded mechanically the blood flow through the vena cava and, in other experiments, through the aorta. Shock resulted in either case after the obstruction to the circulation was removed. They produced shock also by large doses of adrenalin and by intestinal manipulation. By each of these methods in a large series of tests, they found a marked reduction of plasma volume, accompanied by hemoconcentration, as a regular feature. They regarded reduced plasma volume as the essential feature in the mechanism of shock, and attributed it and the hemoconcentration to transudation of plasma into the tissues. It was evident that retardation of the circulation, either mechanically or from maximal arterial constriction by adrenalin, produced anoxia in the tissues. It has been shown that capillaries become dilated, and their walls become abnormally permeable to colloids, when deprived of an adequate supply of oxygen.

Mason and associates produced shock in dogs by the autolysis of liver substance in vivo. Increased concentration, decreased plasma volume and delayed coagulation of the blood occurred regularly. Observations such as those cited led Moon and Kennedy to test the concentration of the blood in shock, occurring clinically or produced experimentally. Finding that

hemoconcentration appeared early before changes in blood pressure occurred, and that it increased progressively as shock developed, they used it as a criterion of the presence and of the degree of shock in all subsequent studies. They reported on the practical application of this simple test to clinical use in cases of poisoning, infections of unusual severity, hemorrhagic pancreatitis, eclampsia, and of burns. These died of circulatory failure and the blood was highly concentrated as shown by specific gravity, hemoglobin content and erythrocytosis. They concluded that hemoconcentration is proportional to the degree of shock, that it is of value in detecting that condition clinically, in estimating the degree of it and in differentiating it from hemorrhage.

Coonse and his associates corroborated Moon's observations in experimental shock and confirmed the fact that hemoconcentration is characteristic of that condition, while after hemorrhage the blood is diluted.

Blalock and associates found increased concentration of the blood during shock induced by trauma to muscles, by burns of the skin and by intestinal manipulation. They attributed it to local leakage of plasma into and about the areas of injury. Harkins reported nine cases of mesenteric vascular occlusion resulting in shock. He found the hemoglobin was 143 per cent and the hematocrit reading 61, although no vomiting had occurred, in one case. No blood studies were made in the others. Harkins and Harmon reported experiments on animals and observations in human cases, in which hemoconcentration was noted, associated with shock-like circulatory deficiency. This occurred after burns, freezing, bile peritonitis, tissue autolysis in vivo, acute pancreatitis, pulmonary edema, intestinal manipulation, mesenteric and portal obstruction, intestinal strangulation and after the release of an extremity from a constriction. They investigated also the shock-like circulatory failure which develops incident to acute peritonitis, experimentally produced. They found the bleeding volume and the concentration of the blood were like those produced by other vascular poisons such as histamine. Andrews, Harkins, Harmon and Hudson produced shock by subcutaneous injections of bile in dogs. These developed symptoms of surgical shock, ending in death. There was a marked increase in the volume of red cells, shown by hematocrit readings, in every case. They recorded marked local swelling and transudation of fluid about the site of injections, but neglected to record observations on the appearances of the viscera.

The authors quoted in the preceding paragraph adhere to the interpretation that *local* transudation of plasma into the tissues about the injured area causes the abnormal concentration of blood, and that shock is due entirely to such local loss of blood and/or fluid. This interpretation is contrary to the evidence of increased capillary permeability in *systemic* areas, shown in vivo and post mortem. Injections of colloidal dyes, such as trypan blue, are used extensively in studies on capillary phenomena. Such dyes are retained in the circulation under normal conditions, but they escape and

stain the tissues where capillary permeability is increased. When trypan blue is injected intravenously during the development of shock, the staining is not limited to the injured areas but involves viscera areas remote from the injury. Also examinations of the viscera, after death by shock, show wide-spread capillary dilatation, stasis and petechiae in the lungs, mucosae, serosae and in parenchymatous organs. Although these observations on the pathology of shock were published years ago, many workers apparently are not cognizant of them (Moon).

Kopp and Solomon observed a decrease in the plasma volume and an increase in hematocrit readings during shock resulting from therapeutic hyperthermia. At post mortem in one fatal case the congestive, hemorrhagic and edematous changes in lungs, gastrointestinal tract and elsewhere, agreed with those noted by Hartman and Major in two similar cases, and with the pathology of shock as stated by Moon. They attributed the circulatory failure to decreased blood volume, increase in the vascular stream bed and increased vascular permeability.

Scudder and his associates investigated the increased potassium content of the blood in shock resulting from various causes. Incidentally they noted that this was accompanied by a rise in the specific gravity of the whole blood and by an increased volume of red cells. These changes were noted in shock produced by trauma, by intestinal obstruction seen in clinical cases and by experimental intestinal obstruction in animals.

Walther noted concentration of the blood and loss of plasma as characteristics of true shock. He observed that the hemoconcentration subsided when recovery from postoperative shock occurred. Allen produced shock in rats by obstructing, with a rubber band, the circulation of a leg. After five or six hours of obstruction, the removal of the tourniquet was followed by the development of shock. In these experiments Allen used hemoconcentration as a criterion of shock. The red cells progressively increased from 8 million to 10, 11 or 12 million at death. It was noted that the blood was dark and thick and that clotting was delayed.

Eppinger gave detailed consideration to circulatory collapse developing in a wide variety of clinical conditions. They included trauma, burns, severe infections, poisoning with various drugs and from food, sun burn, toxic jaundice, diabetic coma, urticaria and others. The total volume of blood was decreased in such cases. In each instance he found that the heart was not dilated but, on the contrary, was smaller than normal. This resulted from the diminished volume of blood and from decreased return of venous blood to the heart. He found hemoconcentration in all cases of shock or collapse regardless of the condition causing it. This was explained as due to increased permeability of the capillary membranes, with resulting leakage of plasma into the intercellular spaces.

Many of the conditions seen clinically were reproduced in dogs, and the physiologic disturbances were of the same kind as seen in man. Microscopic studies of various tissues showed albuminous fluid in the intercellular

spaces regularly. This fluid had a high protein content like that of the blood plasma. The increased permeability of the endothelium, which resulted in a leakage of plasma and in hemoconcentration, was regarded as of such essential importance that it constituted the title of his monograph "*Die seröse Entzündung.*"

Although the term "serous inflammation" was used by Rössle to designate the presence of serous fluid in intercellular spaces unaccompanied by leukocytic infiltration, its use in such a sense is questionable. The presence of leukocytes is usually regarded as a *sine qua non* of inflammation, and the term edema is used by other pathologists to designate the feature which Rössle described. The fact that the fluid has a high protein content does not make the word edema unappropriate. It is feared that the term "serous inflammation," as applied to this condition, may contribute to confusion rather than to clarification. Notwithstanding this deviation from accepted terminology, Eppinger's observations and deductions are highly significant.

Seeley, Essex and Mann produced shock in dogs to determine the contributory effects of various anesthetics. They recorded hemoconcentration in each instance.

Blood Concentration after Burns

The earliest observations on hemoconcentration which I have found were made in clinical studies on patients suffering from extensive burns of the skin. Baraduc (1863) noted in such cases that the blood was dark, thick and that it failed to clot. He believed this change was related to the mechanism by which death occurred; that the thick viscid blood could not circulate through the minute vessels and that this resulted in death by circulatory failure. Tappeiner (1881) reported counts ranging from 7,810,000 to 8,960,000 in from 6 to 17 hours after burns in four cases which resulted fatally. Wilms (1901) confirmed the previous observations and recorded cell counts ranging from 6,500,000 to 8,200,000 in six persons severely burned. Locke (1902) reported blood counts in ten such cases. The highest count in four non-fatal cases was 7,266,000 while in five of the six fatal cases the erythrocytes were above 9,000,000. He recorded that the blood was dark and thick. Becky and Schmitz, Underhill et al., Simonart, Moon, Wilson et al., Harkins and others have confirmed that marked hemoconcentration occurs immediately after severe superficial burns of the skin.

Underhill and his associates reported blood studies in 20 cases of severe superficial burns. Marked hemoconcentration was found in each instance as indicated by hemoglobin percentages ranging from 114 per cent to 226 per cent. The higher concentrations were found in the more severe cases. The condition was associated with a decreased return of blood from systemic areas, and decreased volume output of the heart. This resulted in systemic anoxia, lowered metabolic processes, low arterial pressure and final

suspension of vital activities. He believed that hemoconcentration is a prime factor in the development of shock from burns. He stated that the degree of concentration is an index of the patient's condition, that neither man nor animals can long survive hemoconcentration of 40 per cent and that the condition becomes precarious at 25 per cent.

Wilson and associates corroborated the fact that shock following burns is indistinguishable from that which results from severe trauma. They saw no reason to doubt that the etiology is similar. They noted that, in shock following burns, there develops a toxemic stage which resembles violent poisoning. In their cases the increase in the hemoglobin ranged from 15 to 150 per cent.

Ebbecke showed that any type of injury to cells, whether thermal, chemical or mechanical, causes them to release a cytoplasmic substance which produces dilatation and permeability of the adjacent capillaries. This results in local edema due to leakage of fluid from the blood into the tissues. If the injury is small and local, this effect is likewise local; but if the injury is extensive, much of the cytoplasmic substance may be absorbed and may produce a similar effect on the minute vessels in systemic areas. This results in a systemic disturbance of the circulation, characterized by low blood volume, increased concentration, reduced return of venous blood from systemic areas, and consequent low cardiac output. He drew a significant comparison between the capillary phenomena about local injuries and those in shock. If one understands the mechanism by which wheals are formed in the skin by mechanical injury, burns, histamine, peptone or anaphylaxis one likewise understands shock produced by extensive trauma, burns, histamine, peptone or anaphylaxis. They result from identical capillary reactions, the one in local areas, the other in visceral or systemic areas.

The researches of Lewis on vascular phenomena in the skin corroborated and extended somewhat those of Ebbecke. He demonstrated that substances released by cells in response to injury affect the capillaries as described by Ebbecke. He called these "H-substances" because of the similarity of their effects to those of histamine. He endorsed the interpretation that the absorption of such substances in large amount produces systemic circulatory disturbances. "These effects lead to an impounding of the blood in the capillary reservoir accompanied by a serious loss of blood fluids into the tissue spaces. Owing to this diversion of the blood the central vessels are depleted, a profound and lasting fall of blood pressure follows, leading to a condition of collapse." Krogh endorsed this explanation of the circulatory collapse which results from extensive superficial burns.

This interpretation is further corroborated by the finding post mortem of effusions in the serous cavities, marked congestion of the minute vessels in visceral areas, ecchymoses indicative of capillary injury, and edema of the lungs, gastrointestinal mucosae and meninges after burns. (Schjer-

ning, Bardeen, Pack, Moon and others.) Such findings indicate that the hemoconcentration is not due entirely to local transudation in and about the injured areas.

Allergic and Anaphylactoid Conditions

Hemoconcentration has been noted by several observers in the group of conditions associated with hypersensitivity to various proteins. Dean and Webb made observations on changes in the blood of 33 dogs during anaphylaxis. They recorded a rise in the hemoglobin content and red cells after the injection of horse serum into sensitized dogs. The hemoconcentration seemed to be proportional to the severity of the symptoms. Simonds found an increased blood concentration and a reduced total blood volume during anaphylactic shock in dogs. Similar findings were recorded after injections of peptone. In this connection it is of interest to recall Dale's observations on the effects of histamine. Although it has not been proved that histamine itself is the cause for either anaphylactic shock, traumatic shock or peptone poisoning, it is believed that the mechanism of the effects is identical.

Underhill et al. compared the effects of histamine with those of Vaughan's crude soluble poison and those of peptone. Each of these caused an immediate fall in blood pressure when injected, and after each there was marked hemoconcentration. Vaughan's soluble poison, which is derived by partial hydrolytic cleavage of protein, produced the severest effects in this comparison. Underhill interpreted these effects as the result of capillary damage.

Cantacuzene found that large doses of hemolytic serum (rabbit hemolysin) caused immediate death when given intravenously to rabbits. Minute doses (0.03 to 0.1 c.c.) caused acute erythrocytosis ranging from 8,000,000 to 9,000,000.

Eppinger noted hemoconcentration associated with urticaria in one case. The red cell count rose from 4,400,000 to 5,700,000 at the height of an urticarial eruption. Black and Kemp induced an acute allergic response by instilling pollen into the nostrils of a sensitive person. This was accompanied by an increase in the specific gravity of the blood from 1.0561 to 1.0578. They found a similar increase in the density of the blood in 18 guinea pigs during anaphylaxis. It was stated that the degree of this increase was roughly parallel to the intensity of the reaction.

It is recalled that anaphylaxis is a true example of shock. Manwaring stated the belief that endothelial permeability is the dominant physiologic change in all types of protein sensitization and that all other anaphylactic reactions are secondary to this. Seegal's review of the subject led to the conclusion that the manifestations of anaphylaxis are referable to one or the other of two causes: contraction of smooth muscle, and increased capillary permeability. Lewis has emphasized the latter as the major factor and attributes it to the release of H-substance incident to the meeting of antigen and antibody within the tissue cells.

Although the mechanism of anaphylaxis has not been explained fully, it is apparent that increased endothelial permeability is a major associated feature. The hemoconcentration which has been observed in histamine and peptone poisoning and following injections of other protein cleavage products, is present also in anaphylactic and allergic states. This appears to be due to abnormal permeability of capillary endothelium.

Poisonous Substances

Krogh showed that capillaries may be injured directly by various substances, and Landis showed that any agent or condition injurious to capillary endothelium renders it abnormally permeable to the fluid of the blood. Sollmann stated that irritant or corrosive poisons cause extensive vascular dilatation in visceral areas, and that death may occur from shock incident to this effect before the symptoms characteristic of that poison have time to develop. Eppinger included poisoning with veronal, mercuric chloride and other poisons in his observations on shock. He noted that decreased blood volume, decreased volume flow, low blood pressure and hemoconcentration were present in such cases. He attributed these features to endothelial damage resulting in escape of plasma into the tissues. With these facts in mind it is pertinent to consider instances in which erythrocytosis has resulted from the effects of poisons.

It is known that acute poisoning with phosphorus often ends in circulatory collapse. Early observers recorded red cell counts above 8,000,000 in such cases (Taussig, v. Jaksch, Limbeck and others). Silbermann reported on polycythemia in phosphorus poisoning seen clinically in Prague. He stated that the acute effects of phosphorus poisoning include the development of polycythemia. In 34 acute cases the red cell counts were above 6,000,000 and in three cases there were more than 8,000,000. Hemoconcentration in poisoning is usually attributed to dehydration by vomiting. The merits of this explanation will be discussed in a subsequent section. Underhill noted that phosgene, among other lethal gases, caused massive edema of the lungs of those who inhaled it. The blood became concentrated because of damage to the endothelial membranes and the resulting escape of fluid into the pulmonary spaces. In this instance the capillary damage was chiefly in the lungs. The effects of other poisons (croton oil, jalap) may be chiefly in the gastrointestinal tract, and they likewise cause hemoconcentration. In still other instances to be discussed, the capillaries in systemic areas are damaged and the effects on the blood and on the circulation are of a similar kind.

Sollmann states that poisoning with arsenic produces a pronounced and persistent fall in blood pressure. This is not due to cardiac failure nor to vasomotor deficiency but he attributes it to paralysis of the capillaries with resulting loss of blood volume by transudation of plasma. It is recalled that Heubner and also Krogh list arsenic among the "capillary

poisons." Many years ago Rogers observed that arsenical poisoning produced circulatory collapse like that of cholera, accompanied by marked hemoconcentration. Red cell counts above 8,000,000 were noted. He recommended this as a diagnostic sign in arsenical poisoning. The shock-like features which sometimes result from intravenous arsenical medication are well known. Moore recorded weakness, grayish cyanosis, cold clammy skin, nausea, vomiting and syncope as the clinical features in such instances. The blood pressure fell alarmingly and sometimes was unobtainable. He noted further that the blood volume was reduced and that hemoglobin and erythrocytes were correspondingly increased, indicating concentration.

Various organic substances will produce circulatory deficiency of the shock type, accompanied by increased concentration of the blood. Dale and associates showed that in histamine shock the plasma volume is decreased by 50 or 60 per cent and the red cells are correspondingly concentrated as shown by counts, hemoglobin content and hematocrit readings. They explained this as the result of endothelial injury and regarded the effects of histamine as typifying those of other substances such as peptone, products of protein cleavage, bile, bacterial toxins and the like. Peptone shock is accompanied by hemoconcentration (Underhill and Ringer, Simonds, Eppinger, Moon and others).

Injections of bile intravenously, intraperitoneally or subcutaneously, will result in shock. This is accompanied by marked concentration of the blood (Horall and Carlson, Harkins, et al.). Sodium glychocholate will produce similar effects (Moon and Morgan). The venoms of various snakes cause endothelial injury and affect the circulation as does histamine. Marked hemoconcentration is a feature in such experiments (Kellaway, Essex and Markowitz, Moon).

Lipsitz reported a case of accidental poisoning with tincture cantharides. Weak rapid pulse, subnormal temperature, thirst, vomiting and low blood pressure were prominent clinical features. The red cell count reached 10,430,000. This subsided to normal as the condition progressed to recovery. Cantharis, given by stomach tube to rabbits, produced "polycythemia" of several days' duration. In one instance the erythrocytic count rose from 5,560,000 to 9,800,000. Morgulis and Muirhead made further studies on the effects of cantharis on dogs and rabbits, and substantiated hemoconcentration as one of the features. After fatal poisoning the visceral changes noted were identical in kind with those later described by Moon as characteristic of shock.

The shock-like effects of adrenalin were mentioned in a preceding paragraph. Bainbridge and Trevan noted a decrease in plasma volume, increased concentration of the blood and declining blood pressure after the slow injection of large doses of adrenalin in dogs. The circulatory effects were like those of histamine. In one instance the hemoglobin increased from 95 to 120 per cent and the viscosity of the blood rose from 6.8 to

9.1. Edmunds and Nelson, Freeman and others have found that large doses of adrenalin caused hemoconcentration due to loss of plasma volume. Lamson noted a rapid marked increase in erythrocytic counts after injections of epinephrine. He stated that all conditions of acute polycythemia are due to concentration of the blood by fluid loss. This loss might occur: (1) because of endothelial poisoning, as by histamine, with leakage of plasma into the tissues; or (2) local irritation with loss of fluid, as in the diarrhea of cholera or the pulmonary edema of gas poisoning.

Other poisons such as para-phenylene-diamine produce tissue edema and hemoconcentration by increasing endothelial permeability (Hanzlik and Tainter). Kilgor recorded occupational dye poisoning resulting in subnormal temperature and low blood pressure but without diarrhea or vomiting. In one such case with fatal outcome, the count of red cells rose from 4,416,000 to 9,100,000. Hamilton recorded moderate hemoconcentration in several types of occupational poisoning. Davis noted an increase of about 20 per cent in the erythrocytes in experimental sublethal cobalt poisoning in dogs.

The instances cited indicate that a varied group of chemicals and drugs possess the property of causing damage to endothelium. This effect causes circulatory deficiency of the shock type, which is accompanied by hemoconcentration.

Infections and Other Conditions of Intoxication

Circulatory deficiency often occurs as a terminal event in infections of unusual severity. Physicians since early times have attributed this to vasomotor or cardiac deficiency, 'myocarditis' and the like. Romberg and Pässler (1899) were the first to show experimentally that the efficiency of the heart is not impaired in such conditions.

Not many observations on erythrocytosis during severe infections and intoxications have been found. The earliest report I have seen was by Giesbock (1905). He noted that influenza with low blood pressure in young subjects was accompanied by erythrocytosis. The highest count recorded was 8,700,000. A patient with gangrene of the leg was found to have 8,000,000 red cells per cu. mm. Underhill and Ringer reported blood studies in 43 cases of influenza. The hemoglobin content ranged from 110 per cent to 140 per cent in severe cases, all of which ended fatally. There was no instance of hemoconcentration in any patient who recovered. They stated that this feature is a valuable sign in prognosis. Moon recorded red cell counts of 6,000,000 to 8,000,000 in severe influenzal infection.

It is well known that diphtheritic infection may terminate by circulatory collapse. This is usually attributed to myocardial weakness. Brodie (1899) tested the effects of diphtheria toxin in cats. Injections of this caused a decline in blood pressure ending in death. When animals were

dying from a fatal dose, given 36 hours before, he was able to keep the heart alive and beating for an hour or two after the death of the animal by perfusing the heart with defibrinated blood. MacCallum performed similar experiments on dogs with like results and concluded that the working capacity of the heart under the influence of lethal diphtheritic intoxication is as good as that of the normal heart.

Harding made intensive studies of diphtheria as seen in over 800 clinical cases. She noted that the circulatory deficiency seen in the toxemic stage closely resembled that in wound shock. The total blood volume and cardiac output were markedly reduced and hemoconcentration was shown by increased specific gravity and red cell counts. The highest concentration was found in the severest cases. She cited similar observations by others. Marked subcutaneous edema developed in many instances. The edema fluid had a high protein content like that of the blood plasma. This was interpreted as due to abnormal permeability of the endothelium resulting from the effects of diphtheria toxin. Anoxia was assigned as a contributory factor.

Early observers noted that the blood of patients severely ill with cholera was thick, dark and viscid. They attributed this to excessive loss of fluid by diarrhea. Later writers have confirmed this observation and interpretation. Frequently the red cell counts range between 8,000,000 and 9,000,000 (Rogers, Crowell). These authors were able to reduce the mortality from cholera by about 50 per cent by giving repeated infusions of saline solution. This fact indicates that simple dehydration is the chief cause of hemoconcentration, low blood volume and failing circulation in cholera. It also indicates that the mechanisms of circulatory failure in cholera and in other forms of shock are not identical, for when similar hemoconcentration, blood volume and low blood pressure are present in shock from other causes, neither saline solution nor any other fluid is effective. The capillary walls appear incapable of retaining fluid supplied in any form (Keith).

Circulatory failure, having all the features of shock, develops in dogs several days after bilateral adrenalectomy. This is accompanied by hemoconcentration as in other instances of shock. (Swingle et al.; Rogoff and Stewart; Winter and Hartman.) The animals may be restored to a normal physiologic state by injections of adrenal cortical extract, and the blood returns to its normal cellular composition. Rowntree reported on 43 cases of Addison's disease. In advanced stages there was decreased blood volume, progressive decline in blood pressure and other shock-like manifestations. Examination of the blood showed hemoconcentration in several such instances.

Barnard (1907) noted that circulatory collapse is one of the characteristic features resulting from intestinal obstruction. He stated that the blood becomes concentrated and viscid and quoted Nothnagel as estimating a concentration of 24 per cent with a correspondingly high hemoglobin

content. Cope recorded a case in which the red cell count was 7,600,000 although the blood pressure had not as yet declined. He stated that this feature indicated a decreased blood volume, and indicated the onset of shock more reliably than the blood pressure.

The fact that intestinal obstruction causes concentration of the blood has been confirmed by many investigators and is accepted as a characteristic feature, particularly after infarction, volvulus or strangulation. Many writers have explained this as due to dehydration by vomiting and consequent loss of fluid volume from the blood. It may be questioned whether this alone is the entire cause. Moon and Morgan found evidences of capillary injury such as edema, effusions and ecchymoses in extensive visceral areas after experimental strangulation of the jejunum in dogs. The edema fluid had a high protein content like that of plasma. The concentration of the blood was increased by 30–40 per cent. In a few experiments they injected trypan blue intravenously when hemoconcentration was developing. The escape of the dye into various tissues in the thoracic and abdominal regions indicated injury to capillary endothelium in systemic areas.

Another phase of evidence should be considered with reference to dehydration by vomiting. Several workers have shown that prolonged vomiting produced by injections of apomorphine will not reproduce the symptoms of intestinal obstruction in dogs. Morgan and I have made several such experiments incidental to studies on hemoconcentration. Water and food were withheld from dogs for 12 hours prior to and during the experiments. The dogs were weighed carefully, and blood examinations made, immediately before and after the experiments. Apomorphine was given by injection repeatedly until loss of weight ranging from 3 per cent to 5 per cent of the body weight resulted. The vomitus was much more voluminous than we have ever seen result from intestinal obstruction. Yet the blood was not concentrated in the slightest degree after such rapid loss of fluid.

The evidence indicates that loss of fluid by vomiting is not the entire cause for hemoconcentration incident to high intestinal obstruction. It appears that marked loss by vomiting will not cause dehydration of the blood so long as the physiologic mechanism which controls the movement of fluid between the blood and the tissues, is not disturbed in its function. It also appears that extensive injury to endothelium interrupts the operation of this mechanism.

Clinical descriptions of the symptoms and course of acute pancreatitis indicate that severe cases usually develop the shock syndrome. "Of the existence of shock in acute pancreatitis there is never the slightest doubt" (Deaver). Only a few records of red cell counts in this condition have been found. De Takats and Mackenzie reported on the clinical features in a series of 30 cases. Red cell counts had been made in nine of these, and showed concentration of the blood in each instance. The highest

count recorded was 8,300,000, ten hours after the onset of pancreatitis. I have reported one case in which there were 6,400,000 red cells per cu. mm. on admission to the hospital. No subsequent counts were made. The patient died in collapse 48 hours later and the necropsy findings were those which characterize shock.

Circulatory failure or collapse sometimes occurs as a terminal event in the toxemias of pregnancy. Adair and Stieglitz stated that this is similar to surgical or anaphylactic shock. De Lee confirmed the occurrence of circulatory failure resembling shock as a grave complication of pregnancy. He recorded a red cell count of 9,000,000 in one such instance.

The Mechanism of Shock and of Compensation

The circulatory deficiency, which manifests itself in the syndrome of shock, results from a disparity between the volume of blood and the volume capacity of the vascular system. That disparity may originate in either one of two factors, usually in a combination of the two. These factors are: (a) conditions which tend to reduce the volume of blood and (b) those which increase the volume capacity of the vascular system.

(a) The important conditions which tend to decrease the total blood volume are: direct loss of blood by hemorrhage, loss of fluid by perspiration, vomiting and purging, loss of plasma by transudation about the injury and in visceral areas as edema and serous effusions.

(b) An increase in the volume capacity of the vascular system may result from dilatation of any part of it. The heart, arteries and arterioles have not been found dilated in shock from any cause. The large veins are flaccid and only partly filled, but the capillaries and venules are found engorged and greatly distended. It appears that dilatation of these, in extensive visceral areas, is the chief factor causing increased volume capacity of the vascular system.

The physiologic mechanism by which decreased blood volume is compensated and disparity prevented, likewise consists of two main factors: (a) Reduction of the capacity of the circulatory system and (b) restoration of lost volume.

(a) The volume capacity of the vascular system is reduced physiologically by constriction of its various parts. Apparently this is a vasomotor reaction affecting the arteries, veins, heart and reservoir organs especially the spleen. The heart is decreased in size as shown by roentgen-ray and by diagraphic measurements (Eppinger). The arteries are maximally contracted and the spleen is reduced in size. The peripheral veins become collapsed and bloodless so that sometimes it is difficult to obtain blood by venepuncture. Under normal conditions the capillaries and venules may be constricted likewise but under adverse conditions, including the effects of poisons, toxins, irritants and even partial anoxia, the capillaries may become atonic and unresponsive to stimuli which cause normal capillaries to contract.

(b) The reactions which tend to restore the reduced volume include the discharge of blood from reservoirs, such as the spleen, and the absorption of fluid from other sources. The latter is the chief means for compensating loss of blood volume. It includes the fluid absorbed from tissues, resulting in their relative dehydration, and that supplied through the natural route—the gastrointestinal tract.

The same mechanism of compensation is operative after loss of blood by hemorrhage and in the circulatory deficiency of shock. Under normal conditions a moderate loss of blood volume as by hemorrhage is quickly compensated. But when damage to capillary endothelium has occurred there is a serious disorganization of physiologic processes. Some of the forces concerned with the movement of fluid into the tissues from the blood, and vice versa, are capillary blood pressure, molecular and ionic concentration, electric potentials, hormonal substances and osmotic pressures. These forces are concerned in the maintenance of "water balance," of blood concentration and volume. Their physiologic action is conditioned upon the presence of a normal semi-permeable endothelium between the blood and the extra-vascular fluids and tissues. Alterations in the condition of the endothelium disturb seriously the physiologic mechanism (Landis) and interrupt the processes described. Under such conditions the process of absorption is reversed. Instead of gaining fluid to restore lost volume, the blood actually loses fluid which is demonstrable as edema and effusions.

Fluid is lost also by vomiting, purging and perspiration. But, except under extreme conditions such as the diarrhea of cholera or after prolonged deprivation of water, this loss of fluid is at the expense of the tissues. Profuse vomiting, produced by apomorphine in animals, does not increase the concentration of the blood, nor is it affected by catharsis, by saline purgatives or by castor oil. Hunt found no change in the concentration of the blood when marked loss of weight resulted from perspiration in a Turkish bath. Cohn found that profuse perspiration incident to muscular exertion did not increase the hemoglobin content of the blood.

The blood is maintained at a remarkably constant level of concentration so long as the forces concerned with preserving fluid balance have a normal endothelial membrane through which to operate. The effects of various noxae upon capillary endothelium destroy its function of maintaining a physiologic differential between the composition of the intra- and extra-vascular fluids. These effects not only stop the machine, they wreck the machinery.

Bazett, in analyzing the mechanism of compensation, recognized damage to the capillary walls and anoxia as important factors in producing irreversible circulatory deficiency. The speed of the collapse and the rapidity of declining blood pressure, when compensation fails, were described as striking phenomena. The precipitous decline in blood pressure incident to failing compensation is shown in charts 1, 2, 3 and 5.

Additional Evidence

It was thought pertinent to produce damage to endothelium in extensive areas by various agents and to note the effects on the concentration of the blood. In some instances continuous blood pressure readings were made for comparison. One method was as follows: A normal dog was anesthetized and bled to death. A quantity of muscle was excised from the thighs and was ground finely in a meat chopper, weighed and suspended in saline solution. Aseptic precautions were employed throughout. A normal dog was held under continuous ether anesthesia through a tracheal tube, and a mercury manometer was connected to a canula in the carotid artery. Minced muscle substance, 4.0 gm. per kg. of body weight, was introduced directly into the abdominal cavity through a short incision.

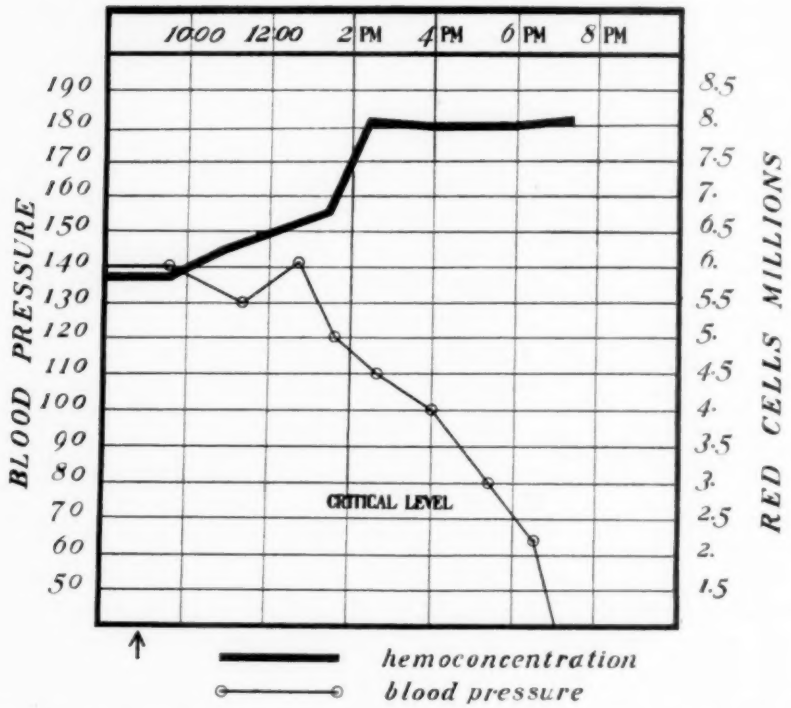

Chart 1. Curves of hemoconcentration and blood pressure during the development of experimental shock in a dog. Blood pressure in mm. of mercury is shown at the left, red cell counts in millions at the right, and clock time at the top of the chart. Muscle pulp was placed in the peritoneum at 9:00 a.m. (indicated by arrow). A temporary decline in blood pressure between 9:40 and 11:20 probably indicates the effect of decreasing blood volume and increasing volume capacity of the vascular system. The rising arterial pressure between 11:20 and 12:45 indicates effective compensation. The hemoconcentration reached its maximum at 2:20, 3½ hours before the blood pressure declined to the critical level. Then the pressure fell precipitately indicating total decompensation. Death occurred at 7:20, about 10½ hours after the experiment was begun.

The conditions of this experiment were arranged to approximate those

of shock developing from an extensive injury to muscles in man. There was opportunity for absorption of cytoplasmic substances emanating from the mass of damaged muscle tissue in the peritoneal cavity.

Counts of the red cells and hemoglobin determinations were made immediately before and at intervals after the operation. Progressive concentration of the blood began almost immediately and had reached a degree of over 15 per cent three hours later, at which time the blood pressure was at its highest point. The hemoconcentration had reached its maximum almost four hours before the blood pressure had declined to a critical level (70 to 80 mm. of mercury). The curves of the hemoconcentration and blood pressure are shown graphically in chart 1. Repetitions of this experiment gave uniformly similar results. In every instance the maximum concentration of the blood occurred several hours before the blood pressure sank to the critical level.

I have had opportunity to compare hemoconcentration with blood pressure readings in a number of clinical cases during the development of circulatory deficiency of the shock type. In each instance examination of the blood forecast the development of shock several hours to several days before the blood pressure declined notably. A few instances will be cited.

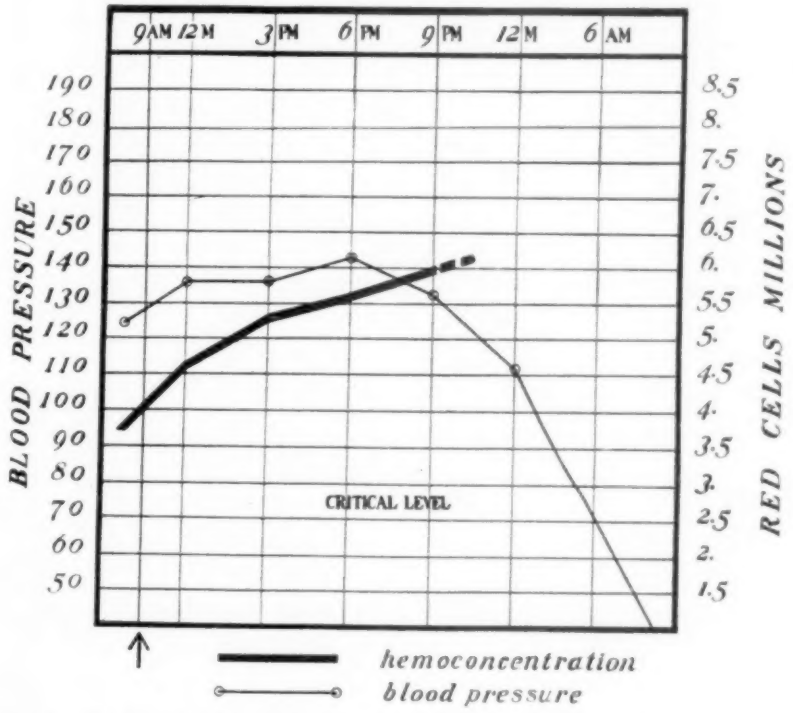

CHART 2. Curves of hemoconcentration and blood pressure during the development of surgical shock. In this instance the concentration of the blood indicated impending circulatory deficiency at 12:00 m., which was 12 hours before the arterial pressure gave a similar indication. The mechanism of compensation apparently was adequate until about 9 p.m., by which time hemoconcentration of 60 per cent had developed.

A white woman 54 years of age had been prepared for colonic resection by a previous colostomy operation. The resection under ether anesthesia was begun at 8:00 a.m. and was finished in 35 minutes. The patient's condition as indicated by pulse, respiration and blood pressure was satisfactory on return to her room. The blood pressure was not only well maintained, it actually *increased* for several hours, so that at 6:00 p.m. it was at its highest point. Meanwhile hemoconcentration had developed steadily (chart 2). The erythrocytic count rose from 3,820,000 before the operation to above 5,500,000 nine hours later—a concentration of more than 50 per cent. The concentration of the blood three hours after the operation forecast the impending circulatory collapse 12 hours before compensation failed. Death occurred by shock 26 hours after the operation.

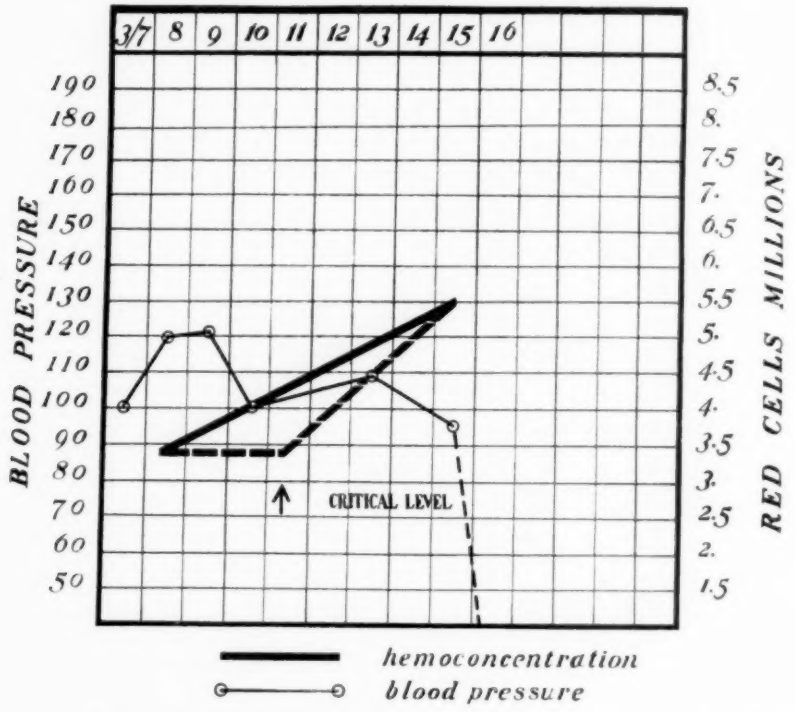

CHART 3. Curves of hemoconcentration and arterial pressure in shock of gradual development. Time is shown in days. Colostomy was done on March 11 (arrow). Only two counts of erythrocytes were made. The heavy solid line connects them. It is probable that the heavy broken line represents the actual course of the concentration. The arterial pressure was at 96 mm. at noon on March 15, the last reading recorded. Decompensation probably occurred about that time. Death occurred at 2:00 a.m. on the sixteenth.

In another instance a woman was admitted to the hospital (March 7) suffering from colonic obstruction. Only two counts of red cells were made: one three days prior to, and another four days after the operation (chart 3). The heavy solid line, March 8 to 15, indicates the degree of

concentration. However, the heavy broken line is the more probable curve, since there was no reason for an increased cell count prior to the operation (March 11). In this instance the concentration of the blood gave warning of circulatory deficiency four days before the blood pressure began its final decline.

In another case, rectal resection for carcinoma, hemoconcentration of 40 per cent occurred within a few hours, while the blood pressure was at its highest recorded point (chart 4). Transfusion of blood and repeated

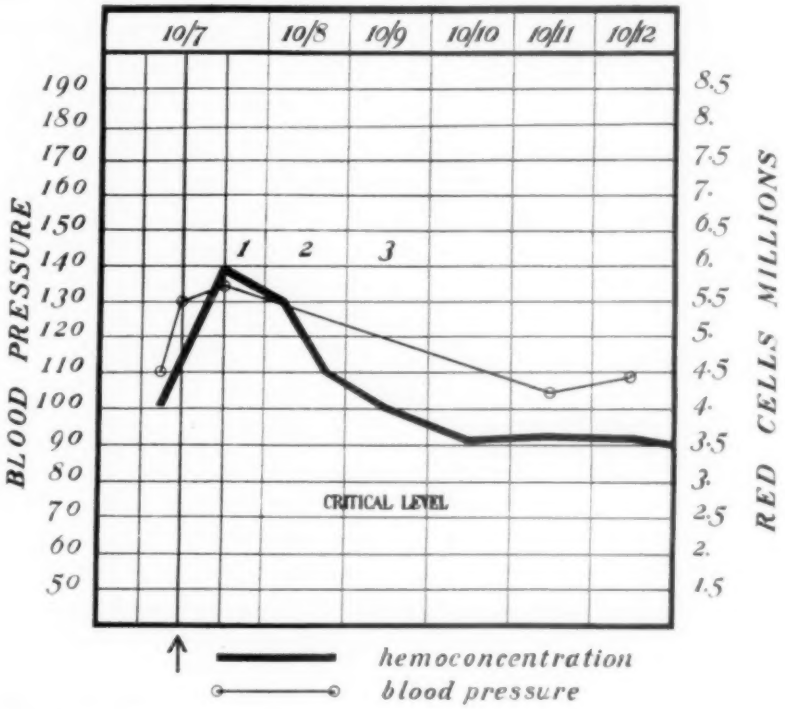

CHART 4. Curves of hemoconcentration and blood pressure after operation (rectal resection for carcinoma, arrow) followed by recovery. Note the immediate rise in concentration indicating the imminence of circulatory failure, and the accompanying rise in arterial pressure indicating active compensation. Transfusion of blood and glucose-saline solution intravenously were given after the operation and on the next day (1 and 2). Saline hypodermoclysis was given on the following day (3).

intravenous infusions of glucose-saline solution after the operation and on subsequent days were followed by recovery.

Circulatory failure incident to systemic intoxication was illustrated by an instance of icterus gravis, with fatal termination on the sixth day of hospitalization. The blood count on May 28, the day after admission, was 4,490,000. Two days later it had risen to 6,240,000—an increase of 40 per cent. During this time the blood pressure *rose* from 110 to 130 mm. of mercury. Two days later the blood pressure had declined only to 120 but

the decline continued precipitately, ending in death (chart 5). Hemoconcentration in this instance preceded the circulatory collapse by two days, during which time the blood pressure gave no intimation of impending failure of compensation.

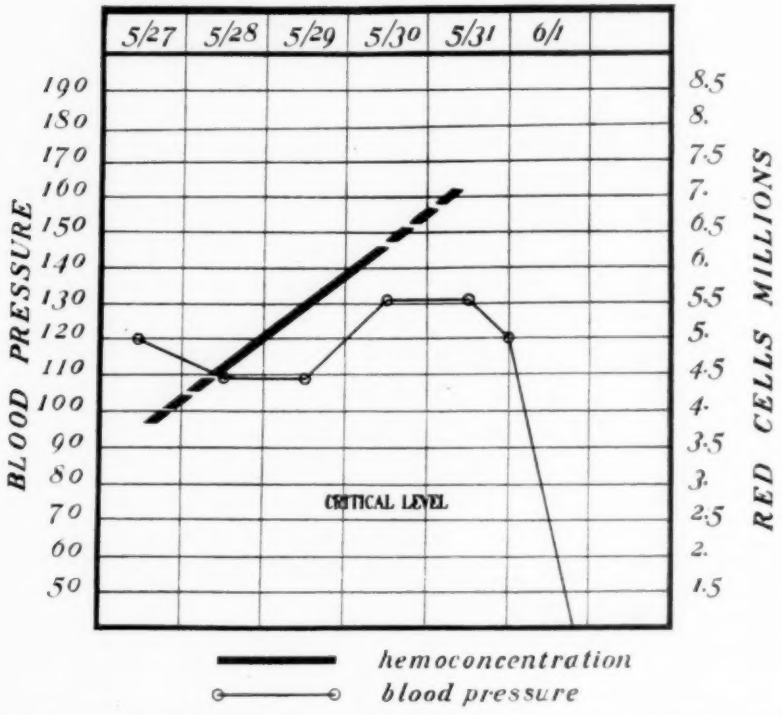

CHART 5. Curves of hemoconcentration and blood pressure during circulatory failure incident to icterus gravis. Time is shown in calendar days. Only two counts of erythrocytes were made. The heavy solid line connects them. In this instance hemoconcentration of 40 per cent was accompanied by a compensatory rise in arterial pressure, and occurred two days before death. Note the precipitate fall in blood pressure when compensation failed.

I have performed or supervised numerous experiments in which data on the hemoglobin and red cell content of the blood were obtained with scrupulous care. Hemoconcentration was used in several series as a criterion of the development and of the degree of shock produced experimentally. In other series the effects of various substances upon the concentration of the blood and upon the circulation were studied. Many of the results have been published and some await publication. The features of these experiments which bear upon the significance of hemoconcentration will be summarized briefly.

The experiments included: finely ground normal tissues, such as muscle, liver, kidney and others, introduced intraperitoneally; watery extracts and autolysates of normal tissues given intravenously or intraperitoneally; bile and its salts, peptone, bacterial cultures and toxins, histamine, moccasin

and rattlesnake venoms and emetin injected intravenously or intraperitoneally; barbiturates given by mouth or by injection; burns, trauma to muscles, intestinal manipulation and strangulation produced under ether anesthesia; and the effects of normal horse serum in sensitized animals.

Such experiments were done on 147 dogs, 98 guinea pigs, 36 cats and on smaller numbers of rabbits, rats and monkeys. Regularly and without exception, the agents and conditions mentioned produced hemoconcentration in each animal and species. This appeared immediately and its degree was proportional to the apparent severity of the accompanying illness.

When recovery followed, the blood returned to its normal corpuscular composition. When death resulted, the postmortem findings regularly showed evidence of capillary damage in visceral areas. This evidence included serous effusions, dilatation of capillaries and venules with apparent stasis of blood in them, ecchymoses and edema in various tissues. The edema fluid was shown to have a high protein content.

The evidence summarized from published reports indicates that acute erythrocytosis is etiologically related to the mechanism by which circulatory failure or collapse develops in a wide variety of clinical conditions. Most authors attributed this directly to the leakage of fluid through endothelium which has been rendered abnormally permeable by injury. Landis' studies on capillary phenomena indicate that any agent or condition injurious to capillaries increases the permeability of the endothelium.

The experiments and clinical observations which I have recorded furnish direct support and confirmation for the interpretations just given. Landis stated that the development of capillary stasis, seen in living tissues, is the surest sign of endothelial permeability. It may be stated with equal assurance that *hemoconcentration is the surest and earliest clinical sign of endothelial permeability* sufficient in degree or extent to affect the efficiency of the systemic circulation.

It is strange that a phenomenon which is so grave in its import, so common in its occurrence and so easily demonstrated, has not been utilized by physicians in their clinical study of patients.

Summary

Reported observations on hemoconcentration indicate that this phenomenon occurs rather frequently in grave conditions of disease quite diverse in origin. Undoubtedly this survey is far from complete, but the number of instances found is sufficiently large and diversified to justify a summary of the authors' observations and interpretations.

It appears that hemoconcentration is regularly associated with a type of circulatory deficiency in which loss of plasma volume is the essential feature.

The loss of fluid may result either from endothelial damage which allows for leakage of plasma into the tissue spaces, or from dehydration incident to vomiting, diarrhea and perspiration.

This loss may be compensated in part by absorption of fluid from the tissues and in part by constriction of the vascular walls, especially the heart, arteries and spleen and, to a lesser degree, by constriction of the veins and capillaries.

So long as the mechanism of compensation is effective, no marked deficiency is evident. When compensation becomes inadequate, the blood pressure declines progressively, anoxia develops and the syndrome of shock is manifested.

So long as the vascular endothelium is able to perform its part in the maintenance of fluid balance, there is dehydration of the tissues but not of the blood. In advanced stages of shock the vascular system is neither able to absorb nor to retain fluid. It appears that the critical point in this mechanism is the physiologic state of the vascular endothelium.

This type of circulatory deficiency may develop whenever and however the capillaries in an extensive visceral area are rendered atonic.

A rising curve of concentration is as ominous as a falling curve of arterial pressure. But the former occurs early and indicates the developmental stage of circulatory deficiency while the latter indicates the failure of compensation and the imminence of death.

Circulatory failure in its *incipient* stage may be recognized by the presence of hemoconcentration. This feature is of inestimable practical value, for treatment must be applied early, otherwise it will be ineffective.

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BACTERIOLOGY OF ENDOCARDITIS WITH REPORT OF TWO UNUSUAL CASES *

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Since 1900, every review [1, 2, 3, 4, 5] of the exciting causes of bacterial endocarditis has always included the *Streptococcus, hemolyticus* and *mitior, Diplococcus pneumoniae,* the *Hemophilus influenzae,* the *Staphylococcus aureus* and the *Neisseria gonorrheae.* These organisms no longer arouse comment when found. However, it is still unusual to see cases due to other bacteria and this report concerns itself mainly with the rarer forms of bacterial endocarditis.

A review of the literature reveals reports of many isolated cases of endocarditis due to organisms ordinarily considered non-pathogenic, some of cases due to organisms pathogenic for man but rarely involving the heart, and finally, a few cases caused by organisms which defy classification. These observations are not new, for Horder [2] in 1909 noted that "micro-organisms difficult to classify are not seldom obtained from cases of endocarditis even during life." It is still true, however, that when compared with the common causative bacteria the incidence of the rarer forms is extremely low. Yet one cannot agree with Blumer [5] who states that "so few other organisms have been described during the era of modern clinical bacteriology that we are constrained to believe that some, at least, of the older observations concern accidental contamination or terminal invaders rather than the true cause of the disease." Careful bacteriological investigations in any active clinical laboratory not infrequently isolate unclassified organisms as causative factors in different types of infections.

Many organisms have been described in the literature. Only those cases with careful antemortem and postmortem bacteriological studies have been included. No attempt has been made to record the innumerable varieties of streptococci reported. Organisms which have been described include the following:

Streptococceae—Streptococcus mitior
Streptococcus pyogenes
Diplococcus pneumoniae [6]

Neisserieae—Neisseria gonorrheae [7]
Neisseria intracellularis [8]
Neisseria catarrhalis [9]
Neisseria sicca [10, 11, 12]
Neisseria flava [13]

* Received for publication December 1936.
This investigation was carried out at the Pathological Laboratories of the Boston City Hospital in 1931–1932. Thesis presented as partial requirement for the degree of Doctor of Medical Science, Columbia University, 1935.

Hemophileae—Hemophilus influenzae [14]
Hemophilus hemolyticus [15]

Micrococceae—Staphylococcus aureus
Staphylococcus albus [2]
Gaffkya tetragena [5]

Bacterieae—Escherichia coli [1, 2]
Escherichia acidilactici [16]
Eberthella typhi [17]
Aerobacter aerogenes [2]

Miscellaneous—Pseudomonas aeruginosa [1, 4]
Bacillus anthracis [18]
Corynebacterium pseudodiphthericum [19]
Actinomycis hominis [20]
Brucella melitensis [21]
Pasteurella pestis [22]
Micrococcus endocarditis rugatus [23, 24]
Unclassified gram negative coccus [25]
Mycobacterium tuberculosis [29]

Some of the rarer organisms mentioned above produced clinical syndromes suggesting acute bacterial endocarditis while others gave rise to the subacute variety. Likewise from autopsy reports, it was apparent that focal glomerular lesions were found in a considerable number of the cases. Both normal and previously damaged valves have been affected by these organisms.

While working in the Pathological Laboratory at the Boston City Hospital, the author had the opportunity to study intensively the antemortem and postmortem bacteriology, pathology and serology of two cases of endocarditis due to unusual organisms. The protocols and bacteriological investigations, together with clinical abstracts, follow.

Case Report

Clinical History: The patient was a 26-year-old white male who entered the hospital in March 1932 complaining of frequent chills of six weeks' duration. One week before admission, when looking for a job, the patient was told that he had a heart murmur. No history of rheumatic fever could be obtained.

Family history and past history were irrelevant.

Physical Examination: The heart was not enlarged. At the apex there was a faint systolic thrill and a harsh rough systolic murmur transmitted to the axilla. The blood pressure was 100 mm. of mercury systolic and 60 mm. diastolic. The spleen was not palpable. The nails were moderately curved.

Laboratory Findings: The urine was normal save for red cells on several occasions. The white blood count ranged around 16,000. Many blood cultures revealed a gram negative diplococcus.

Course: The temperature ranged between 101° F. and 103° F. with corresponding elevation in pulse. The patient had frequent chills followed by profuse sweating

in the evening. On March 18, the patient had sudden pain in the right arm, following which radial and brachial artery pulsations were absent. Ten days later a similar episode involved the right leg. There were numerous abdominal pains suggesting splenic and renal infarcts. At this time, râles were heard throughout the chest. A roentgen-ray was interpreted as revealing bronchopneumonia or metastatic abscesses. The patient became progressively paler and developed a café-au-lait color. Dyspnea increased and became very marked terminally. The patient died seven weeks after admission.

Autopsy

An autopsy was performed April 22, one and a half hours post mortem. The positive findings were as follows:

There is moderate clubbing of the fingers and toes.

The pleural and pericardial cavities contain 200 c.c. and 100 c.c. respectively of clear rusty brown fluid.

Heart: Weight 350 grams. The myocardium and endocardium are essentially negative. The pulmonary, tricuspid, and aortic valves are normal. The free edge of practically the entire anterior leaflet of the mitral valve is eroded and is covered with clusters of large, irregular, friable vegetations. These are also attached to ruptured *chordae tendineae*. The uninvolved portions of the mitral valve are normal in appearance and their *chordae tendineae* thin and delicate. Microscopically the vegetations consist of irregular bands of fresh and hyalinized fibrin in which are clumps of diplococci. These are gram negative when stained by the MacCallum-Goodpasture technic.

Lungs: Both lungs feel firm, resilient and rubbery with a definite diffuse increase in fibrous tissue, more marked at the apices. The sections show a well advanced organizing bronchopneumonia.

Spleen: Weight 200 grams; it is soft and shows large septic infarcts which are soft, yellow, and almost purulent in character. There are also several small healed infarcts.

Liver: Weight 1700 grams. Lobulations are distinct and in places lobules are yellowish gray in appearance. Microscopically the central zone of every lobule involving up to five-sixths of the entire lobule, is necrotic and shows invasion by many leukocytes.

Kidneys: Weight 380 grams. Several small infarcts are noted. Microscopically only one focal glomerular lesion could be found in the four sections studied. Otherwise the sections are not remarkable.

Brain: There is a slight extravasation of blood in the subarachnoid space covering the left occipital lobe.

Vascular System: There is a mycotic aneurysm of the superior mesenteric artery about 3 cm. from its origin. The aneurysmal portion measures about 2 cm. in diameter and is filled with an adherent laminated thrombus. One of the branches, distal to the aneurysm, is filled with greenish pus. Sections show almost complete disappearance of the intima and media, the wall of the aneurysm being made up of a thin layer of necrotic intima and media containing many polymorphonuclear leukocytes and fibrin.

Anatomic Diagnosis: "Acute endocarditis; organizing bronchopneumonia; septic infarcts of spleen; central necrosis of liver; infarcts of kidney; mycotic aneurysm of superior mesenteric artery; subarachnoid hemorrhage."

Bacteriology

Five of six antemortem blood cultures revealed a gram negative bean-shaped diplococcus. Growth was noted after about 48 hours incubation. At the time of autopsy, smears taken from the vegetations, from the septic splenic infarct and

from the suppurative mycotic aneurysm of the superior mesenteric artery revealed a gram negative diplococcus. Three cultures of heart's blood taken post mortem, one about 15 minutes after death, remained sterile but pure cultures were obtained from the lesions noted above. MacCallum-Goodpasture bacterial stains on sections of the vegetations revealed the clumps of organisms to be gram negative with quite a few gram positive organisms of similar morphology scattered through them.

Morphology and Cultural Characteristics: The organism was a small, non-motile, gram negative, biscuit-shaped diplococcus arranged quite often in tetrads and frequently in dense clumps. It varied considerably in size and staining reactions. It grew best on ascitic agar giving rise to round, grayish-white, glistening, smooth, convex colonies with an average diameter of 0.5 mm. The colonies were slightly mucoid, tenacious and adherent to the medium. The microscope showed slight wrinkling of the central portion of the colonies with the periphery perfectly smooth. Only after repeated subculturing on ascitic agar did the organisms grow at room temperature or on plain agar. It did not produce pigment on ascitic agar, blood agar, plain agar and Loeffler's serum medium. In blood broth, it formed a diffuse cloud with a coarsely granular sediment. It was difficult to emulsify and was auto-agglutinable when suspended in saline. It grew slightly under strictly anaerobic conditions.

Fermentation Reactions: These were tested in ascitic peptone broth, containing Andrade's indicator and 1 per cent sugars. Several tests were done with consistent results. Dextrose, saccharose, maltose, levulose, and raffinose were fermented while no change in reaction was noted in lactose and galactose. Final readings were made 14 days after the inoculation of the sugars.

Variability: Cultures were still alive after *seven* days in the icebox and *ten* days in the incubator. Heating for 30 minutes at 55° C. killed the organisms.

Pathogenicity: Heavy saline suspensions of recently isolated cultures were non-pathogenic for mice and guinea pigs when injected intra-peritoneally.

Serology

It was impossible to do agglutination tests with this organism because it agglutinated spontaneously in saline. This made it necessary to do precipitin tests. In all the tests outlined below a carbolized antigen of the various organisms was used. Heavy suspensions of the organisms in 0.5 per cent phenol were incubated for one week at 37.5° C. The suspensions were shaken daily and at the end of one week were centrifuged at high speed. The clear supernatant fluid was pipetted off and made up to 0.9 per cent saline. ("Neisseria pharyngis antigen" refers to the antigen made from the organism isolated from the patient.)

Type 1 *Neisseria intracellularis* obtained from the Commonwealth of Massachusetts Antitoxin and Vaccine Laboratory was used in making up the meningococcus antigen.

The gonococcus used was obtained from the urethra of a patient with chronic gonorrheal urethritis.

In the complement fixation test the serum used was obtained from the patient about one week before death.

In the other tests the serum used was obtained by cardiac puncture just after death and at time of autopsy, one and a half hours post mortem. The polyvalent antimeningococcus serum was obtained from the Commonwealth of Massachusetts Antitoxin and Vaccine Laboratory and the antigonococci serum was obtained from Parke, Davis and Company.

An antiserum was obtained by immunizing a rabbit over a period of six weeks with increasing doses of the organisms. The last dose consisted of living organisms made up of saline washings of the 24 hour growth of four ascitic agar slants injected intravenously. The serum obtained had a precipitin titer of 1–1280 with the carbolized antigen of the organism.

The *Pharyngis siccus* was kindly supplied by Dr. C. W. Rake of the Rockefeller Institute for Medical Research.

The polyvalent gonococcus antigen was obtained from the Commonwealth of Massachusetts Wassermann Laboratory.

Agglutination

The four known types of meningococci were used in an agglutination test with the *Neisseria pharyngis* antiserum. The results were negative throughout.

Complement Fixation

The complement fixation tests were done with one-fourth the quantities employed in the Wassermann test, using 0.5 c.c. of sensitized sheep cells and two units of complement. In each test, patient's antemortem serum was used in the following quantities: 0.1 c.c., 0.05 c.c., 0.037 c.c., 0.025 c.c., 0.013 c.c., 0.005 c.c. The Roman numerals indicate the different tests:

Chart I

Complement-Fixation Tests

Neisseria pharyngis Antigen

I	++++	++++	++++	++++	+++	±
II	++++	++++	++++	++++	+	±
III	+++	+++	+++	+++	±	−
IV	−	±	−	−	−	−
Anticomplementary control	−	−	−	−	−	−

Meningococcus Antigen

I	+++	++	+	±	−	−
II	++	+	±	−	−	−
III	++	±	−	−	−	−
IV	+	−	−	−	−	−
Anticomplementary control	−	−	−	−	−	−

Gonococcus Antigen

I	+	+	±	−	−	−
II	+	±	−	−	−	−
III	+	±	−	−	−	−
Anticomplementary control	−	−	−	−	−	−

In I, 0.05 c.c. of antigen was used throughout with the varying amounts of serum as mentioned above; in II, 0.025 c.c. of antigen; in III, 0.012 c.c. of antigen; in IV, 0.005 c.c. of antigen.

An anticomplementary control was set up similar to I in every condition except for the omission of the antigen.

Precipitin Tests

To test the strength of the various antigens and sera used, the following precipitin tests were done. Undiluted sera were used in all the tests and the titers mentioned refer to dilution of the antigen:

I. *Meningococcus Antigen and Antimeningococcus serum.*
This was positive up to 1–160 with ± at 1–320.

II. *Gonococcus Antigen and Antigonococcus serum.*
This was positive up to 1–160 with ± at 1–320.

III. *Meningococcus Antigen and Antigonococcus serum.*
This was positive up to 1–20.

IV. *Gonococcus Antigen and Antimeningococcus serum.*
This was positive up to 1–80.

Precipitin Tests with Patient's Postmortem Serum

These were done using the various antigens. With the *Neisseria pharyngis* antigen a zone phenomenon was observed. The final titer was 1–160 with ± at 1:200. With the *Neisseria intracellularis* antigen the final titer was 1–20, with the *Neisseria sicca* antigen 1–10, while none was obtained with the *Neisseria gonorrheae* antigen.

Chart II

Precipitin Tests with Patient's Postmortem Serum

Antigen	Final Dilutions of Antigens							Saline	Normal Patient's Serum
	1 : 10	1 : 20	1 : 40	1 : 80	1 : 160	1 : 200	1 : 250		
Neisseria pharyngis Antigen	−	−	+	+	+	±	−	−	−
N. intracellularis Antigen	+	+	−	−	−	−	−	−	−
N. gonorrheae Antigen	−	−	−	−	−	−	−	−	−
N. sicca Antigen	+	−	−	−	−	−	−	−	−

Precipitin Tests with Antimeningococcus Serum

Using the *Neisseria pharyngis* antigen a titer of 1–80 was obtained with antimeningococcus.

CHART III

Precipitin Tests with Antimeningococcus Serum

Antigen	Final Dilutions of Antigen							
	1 10 :	1 : 20	1 : 40	1 : 80	1 : 160	1 : 200	1 : 250	
Neisseria pharyngis Antigen	+	+	+	+	−	−	−	−

PRECIPITIN TESTS WITH ANTIGONOCOCCUS SERUM

A positive precipitin test was obtained with a dilution of the *Neisseria pharyngis* antigen up to 1–80.

CHART IV

Precipitin Tests with Antigonococcus Serum

Antigen	Final Dilutions of Antigen							Saline
	1 : 10	1 : 20	1 : 40	1 : 80	1 : 160	1 : 200	1 : 250	
Neisseria pharyngis Antigen	+	+	+	+	−	−	−	−

PRECIPITIN TESTS WITH *Neisseria pharyngis* ANTISERUM

The antiserum obtained gave a positive precipitin test with a dilution of the *Neisseria pharyngis* antigen up to 1–1280. However, no positive tests were observed in any dilution of the *N. intracellularis* antigen, the *N. gonorrheae* antigen, the *Neisseria pharyngis sicca* antigen and the polyvalent *N. gonorrheae* antigen.

DISCUSSION

The morphological, cultural, and serological characteristics of the organism isolated in this case correspond fairly closely to those of the Neisseria group of organisms. However, it does not agree specifically with any of the standard strains of gram negative cocci as outlined by Elser and Huntoon.[26] It does give the fermentation reactions of *Neisseria sicca*, yet the colony is much smoother and the organisms smaller than the strain of *N. sicca* at our disposal. The investigations of S. P. Wilson [27] and G. S. Wilson and Muriel M. Smith [28] indicate that the classifications of gram negative cocci on the basis of pigment formation, appearance of colonies and fermentation reactions is very unsatisfactory and that after prolonged cultivation these characteristics may change considerably. They propose that the gram negative cocci of the nasopharynx, apart from the *N. intracellularis*, should be classified under a single group, called *Neisseria pharyngis*. The characteristics of this group are defined and we feel that the organism isolated in this case has most of the characteristics assigned to

the group and should be classified with it. There are only five similar cases reported in the literature; in three the organism involved was *Neisseria sicca*, in one *Neisseria flava* and in one *Neisseria catarrhalis*.

Case Report

Clinical History: The patient was a 25-year old Italian male who considered himself quite well until August 1931 when he developed pains in his extremities. In January 1932, he was first seen in the hospital and presented signs of aortic insufficiency and questionable signs of mitral stenosis. He ran a swinging temperature, had a large spleen and clubbed fingers. A diagnosis of bacterial endocarditis was finally made although only one of several blood cultures showed a gram negative rod which was considered to be a contaminant. At that time he showed no signs of myocardial insufficiency. However, he reëntered the hospital in March 1932, complaining of shortness of breath, cough and slight swelling of the ankles.

Physical Examination: The patient appeared ill and was very short of breath. The heart showed tremendous enlargement to the left and some to the right. At the mitral area there were loud presystolic and systolic murmurs, with a to and fro murmur at the base. The liver was enlarged and tender and the spleen was enlarged to percussion. Clubbing of the fingers was quite marked.

Laboratory Findings: The urine on admission showed a slight trace of albumin, 10 red cells and 20 white blood cells per high power field, and a few granular casts. The blood showed a marked secondary anemia; the leukocytes numbered 26,600 per cubic millimeter; polynuclears 89 per cent, lymphocytes 7 per cent and mononuclears 4 per cent.

Course in Hospital: The patient's illness progressed rapidly. He remained very dyspneic and in the last two days became delirious and stuporous. No definite localizing neurological lesions could be demonstrated. The Kahn test was negative. Nonprotein nitrogen was 47 mg. per cent. Blood cultures showed a tiny gram negative diplococcus. The patient died nine days after admission.

Autopsy

An autopsy was performed on April 1, three hours postmortem. The positive findings were as follows:

Rigor mortis has not yet set in. The sclerae show a definite icteric tint. There is moderate enlargement of the lymph nodes in the cervical, axillary and inguinal regions. Clubbing of the fingers and toes is quite marked.

Peritoneal, pleural and pericardial cavities contain 100 c.c., 50 c.c., and 50 c.c., respectively, of clear, straw colored fluid.

Heart: Weight 700 grams. The heart is markedly dilated and considerably hypertrophied. There are many tiny ecchymoses beneath the smooth epicardium. Scattered throughout the flabby myocardium are numerous irregular small patches of silvery scarring. The pulmonary and tricuspid valves are essentially negative. The mitral valve is shortened and thickened with its free margin rolled up. The free borders of the leaflet are covered almost completely by a layer of rough, friable vegetations which extend to the endocardium lining the left auricle and also to thickened *chordae tendinae*, many of which have been ulcerated through leaving their loose ends unattached.

The aortic valve is similarly involved and the cusps, in addition to being eroded, shortened and thickened, are covered along their free borders by vegetations. These are also seen on the intraventricular septum just below the middle aortic cusp. A few endocardial pockets are also seen in this region.

Microscopically the myocardium shows large vascular areas of scarring. The wall of the left auricle is infiltrated with many mononuclears and polymorphonuclears, closely packed in places. Fusing imperceptibly with the underlying endocardium are confluent vegetations made up of an outer shell consisting of masses of organisms plus a few fibrin threads covering a dense collection of polymorphonuclear leukocytes and mononuclears in a network of fibrin. These cells contain numerous intracellular diplococci. The organisms are gram negative when stained by the MacCallum-Goodpasture technic. The aortic and mitral valves are made up of hyalinized connective tissue covered with vegetations similar to those described above.

Lungs: They are boggy and edematous and show a slight terminal bronchopneumonia.

Spleen: Weight 500 grams. It is enlarged and firm and shows a diffuse scattering of irregular, opaque, yellowish-white nodules about 2 mm. in diameter. Microscopically these are infarcts in various stages of organization.

Liver: Weight 2160 grams. Section shows a patchy "nutmeg" appearance. Microscopically one sees a late stage of necrosis involving the central half of practically every lobule.

Kidneys: Weight 600 grams, large and firm. One yellowish-white depressed infarct is noted. In the sections, all the glomeruli show a rather marked increased cellularity and many show focal lesions involving one or more loops.

Brain: In the meninges covering the cortex in the right parieto-occipital region there is a small area of suppuration which extends into the cortex. Microscopically this is made up of a dense collection of polymorphonuclear leukocytes many of which are necrotic.

Lymphoid System: The lymph nodes throughout the body are enlarged and on section appear swollen and edematous. Microscopically the sinuses are distended with numerous large mononuclears which have phagocytosed many polymorphonuclear leukocytes.

Anatomic Diagnoses: Vegetative endocarditis, acute and chronic; sclerosis of myocardium; bronchopneumonia; miliary infarcts of spleen; central necrosis of liver; focal and intracapillary glomerulitis; infarcts of kidney; focal suppurative meningitis; icterus; generalized lymphoid hyperplasia.

Bacteriology

Four blood cultures out of the eleven taken antemortem were positive for a tiny gram negative diplococcus. Growth was noted only after seven days incubation. At the time of autopsy, smears from the suppurative area in the meninges and from the vegetations on the heart valves, revealed a similar organism. *Streptococcus pyogenes* was recovered from a postmortem blood culture but pure cultures of the gram negative diplococcus were obtained from the vegetations and the meninges. MacCallum-Goodpasture bacterial stains on sections of the vegetations revealed the masses of organisms to be gram negative diplococci although many of the organisms retained the gentian-violet dye.

Morphology and Cultural Reactions

The organism is a tiny, nonmotile, gram negative diplococcus arranged most often in dense clumps. It is uniform in size but decolorized with some difficulty. There are also a few gram positive diplococci in the dense clumps of gram negative organisms. It grows best on blood agar giving rise to tiny, smooth, raised, milky, glistening colonies after 24 hours incubation at 37° C. Where the growth is heavy there is a slight amount of greenish discoloration to the medium but the organism is not a true methemoglobin former. It does not grow at room temperature, and no

growth occurs on plain agar or on beef infusion broth. It does not produce pigment. In blood broth it gives rise to a fine granular growth with a heavy granular sediment on top of the blood at the bottom of the tube. It reaches its maximum growth on blood agar on about the seventh day. It is difficult to emulsify and is agglutinated spontaneously when suspended in saline. It grows slightly under strictly anaerobic conditions.

Fermentation Reactions: These were tested in ascitic peptone broth containing Andrade's indicator and 1 per cent sugars. These were done on two different occasions with the same results. Dextrose, saccharose and maltose were fermented while no change in reaction was noted with lactose, raffinose, galactose, and levulose. The final readings were made 14 days after the inoculation of the sugars.

Viability: Cultures were still alive after seven days in the icebox and 10 days in the incubator. Heating for 30 minutes at 55° C. killed the organisms.

Pathogenicity: Heavy saline suspensions of the living organisms injected intraperitoneally into mice and guinea pigs were innocuous.

Serology: An antiserum was made by immunizing a rabbit over a period of six weeks with increasing doses of the organism. The last dose consisted of living organisms made up of the saline washings of the 24 hour growth of four blood agar slants injected intravenously. A positive precipitin test was obtained with a dilution of the antigen up to 1–640.

Precipitin tests done with this serum and *Neisseria intracellularis* antigen, the *Neisseria gonorrheae* antigen, the polyvalent *Neisseria gonorrheae* antigen and the *Neisseria sicca* antigen were all negative. A positive precipitin test was obtained with a dilution of *Neisseria pharyngis* antigen up to 1–20. A precipitin test done with a carbolized antigen of the organism isolated in this case and *Neisseria pharyngis* antiserum was negative in all dilutions.

Discussion

We are at a loss to classify this organism. It has very few of the characteristics of the Neisseria group. There have been very few reports in the literature of cases of endocarditis due to gram negative cocci other than the *N. gonorrheae*, the *N. intracellularis* and the *Neisseria sicca* group mentioned previously. Two cases were ascribed to *Micrococcus endocarditis rugatus* [23] and one to an unnamed organism.[25]

Summary

Two cases of bacterial endocarditis with bacteriological, pathological, and serological studies have been reported together with a review of the literature of the rarer causative agents of this disease. One of the organisms belonged to the *Neisseria pharyngis* group while the other was an unidentified gram negative coccus.

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OBSERVATIONS UPON THE EXPERIMENTAL AND CLINICAL USE OF SULFAPYRIDINE. II. THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH SULFAPYRIDINE *

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The rational utilization of any promising compound in the field of clinical chemotherapy is dependent upon a knowledge of its absorption by, distribution in, and excretion from the body. Early in the course of our studies upon sulfapyridine, we [1] noted that the drug was not readily soluble, and in comparison with sulfanilamide, poorly absorbed, when it was administered to animals by the oral route. While increasing doses gave blood levels of increasing amounts, these concentrations were not at all proportional to the dose, and certain individual animals showed marked variations from time to time in their ability to absorb the drug. It was also observed that the tissues of the host had the power of conjugating sulfapyridine. Later this conjugated fraction was shown by Marshall and his associates [2] and by Baines and Wien [3] to be acetyl sulfapyridine. The results of certain of our studies upon the concentration of the drug in the blood of animals following single doses of sulfapyridine are shown in table 1.

Table I

Blood Levels of Sulfapyridine Following Single Peroral Doses in Mice, Rabbits, Dogs and Man

Species	Dose gm./kilo p.o.	Blood Levels in mg. %, Hours Following Administration of Sulfapyridine															
		1		2		4		5		8		24		36		48	
		F	T	F	T	F	T	F	T	F	T	F	T	F	T	F	T
Mouse	0.5	15.4		15.6		12.5				6.9		3.2					
"	1.0	23.6	22.9			21.1	21.4			16.0	16.5	0.7	0.6			0	0
Rabbit	0.5			2.08	6.3	2.8	7.9			2.9	7.8	T	4.0				
Dog I	1.0	0.8	0.8			6.25	6.25			9.1	9.1	1.0	1.0				
"	1.0					19.4	19.5			16.7	16.8	1.3	1.4				
"	1.0	T	T			9.35	9.44			17.1	17.3	1.2	1.3				
Man	0.05	0.55	0.53			3.26	3.2			2.77	2.6	1.8	1.7	1.1	1.0		
"	0.05	T	T			5.0	4.9			4.1	4.4	2.5	2.6	1.6			
"	0.05	0.5	0.6			4.2	4.0			2.8	3.4	3.1	3.1	1.9	1.9		
"	0.05	1.6	1.7			3.4	3.4			3.1	3.2	3.1	3.1			1.3	1.3
"	0.10	0.9	1.1					4.6	4.6	4.7	7.4	1.9	2.9	0.9	2.4	0.4	0.7
"	0.05 I.V.	5.9	6.6			4.4						0.74	1.23				
Infant	0.1			3.2	3.2	5.6	5.6			5.3	5.4	2.4	2.5			VFT	VFT
"	0.1			4.1	4.1	3.3	3.6			3.2	3.5	2.0	2.3			VFT	VFT

F = Free sulfapyridine
T = Total sulfapyridine (including conjugated fraction)

We next investigated the absorption of sulfapyridine when the drug was given to human beings by the oral route. These studies were carried

* Received for publication July 1, 1939.
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This investigation was supported by a grant from The Chemical Foundation, Inc., of New York City.

out by estimating the concentrations of the drug in the blood following single doses and by determining the amount of sulfapyridine excreted in the urine in a given period of time.

It soon became evident that lower concentrations of the drug were to be found in the blood after a given dose of sulfapyridine than would be expected had the same amount of sulfanilamide been administered. It was also observed, as is shown in table 1, that the concentration of the drug in the blood was maintained somewhat better than is the case with sulfanilamide. This latter factor is probably dependent upon a somewhat slower absorption and less rapid excretion of the drug.

During the past year we have noted marked variations between individuals in their ability to absorb sulfapyridine, and we have also observed similar variations in the same individual when the drug was given over a period of time. Thus, in one instance, an adult receiving a total of 9 grams of sulfapyridine during the first 24 hours of an illness had a concentration of 3.3 milligrams per cent of the free drug with a total of 5.0 milligrams per cent, while another patient of the same weight had a concentration of 9.0 milligrams per cent of the free drug and 11.1 milligrams per cent total following the same dose over the same period of time. Another factor which militated against rational therapy with the drug was the tendency on the part of the tissues of certain individuals to conjugate a large proportion of the absorbed drug to the inactive acetyl derivative. Thus, we have repeatedly noted in certain individuals that despite an adequate absorption of the drug (as measured by the total sulfapyridine content of the blood) satisfactory therapeutic levels of the free drug were difficult to obtain and maintain because from 40 to 80 per cent of the absorbed drug had been conjugated to the acetyl form. This excessive conjugation of the drug may be present from the beginning of therapy or it may become progressively more marked as treatment is continued.

The drug is distributed in transudates and exudates as a general rule in about half to three-quarters of the amounts present in the blood. In chart 1 are shown the blood and spinal fluid values for the drug that were obtained in specimens from a patient who was admitted to the hospital with a presumptive diagnosis of pneumococcal meningitis. (Actually the disease was found to be due to anaerobic streptococci.) This chart also clearly indicates the rapidity with which high concentrations of sulfapyridine may be obtained in the blood and spinal fluid following the intravenous use of the sodium salt of sulfapyridine.

During the past year, various observers have noted that pleural exudates obtained from patients receiving sulfapyridine showed excessively high concentrations of the drug (?) when determinations of these values were made according to the method described by Bratton and Marshall.[4] This gave rise to the supposition that the drug might be concentrated in pleural exudates. During the past winter we made a survey of the possible factors involved in this matter and finally were able to demonstrate that the

local anesthetic, generally procaine hydrochloride (para aminobenzoyl-diethyl aminoethanol hydrochloride), which was used to anesthetize the tissues, was capable of giving a color reaction quite similar to that produced by sulfanilamide or sulfapyridine. This occurs because of the pres-

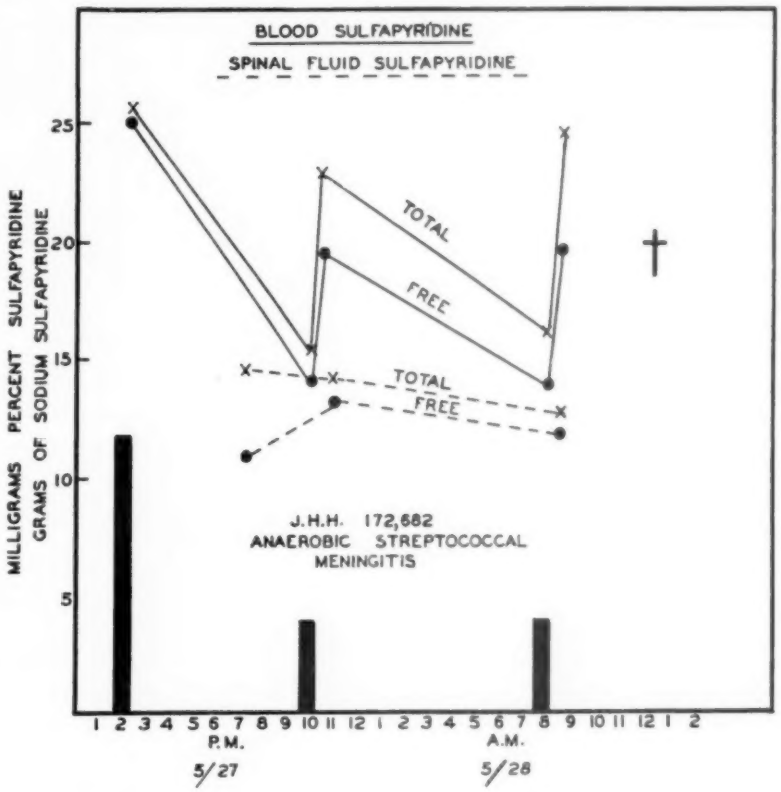

CHART I. The concentrations of sulfapyridine noted in the blood and spinal fluid of a patient receiving sodium sulfapyridine by the intravenous route.

ence of a " free " amino group in this type of local anesthetic. Hence, we feel justified in stating that in our experience the excessive values for sulfapyridine which have been occasionally reported in pleural exudates may result from the contamination of the exudate by a local anesthetic of the procaine type.

As far as we have been able to ascertain, the absorption of sulfapyridine as determined by the amount of drug excreted in the urine, confirms our previous observations on absorption which were based upon its concentration in the blood.

The results of the experiments designed to determine the amount of and rate of excretion of the drug are recorded in table 2. As will be noted, following single doses of the drug, excretion of sulfapyridine is greatest in the first 48 hours, but it may take four days or more to completely rid

TABLE II

Urinary Excretion of Sulfapyridine Following Administration of Single and Repeated Doses of the Compound

Subject	Dose of Compound	Volume of Urine, Excretion in mg. %, Days												Total Drug Excreted	% Dose Excreted
		1			2			3			4				
		U.V. c.c.	F	T	U.V. c.c.	F	T	U.V. c.c.	F	T	U.E. c.c.	F	T		
J. C.	Single 0.05 gm./kilo p.o. Total = 3.0	1875	32.6	48.6	2775	23.5	36.6	1875	11.6	25	1660	6.4	13.2	2.37	79
S. B.	Single 0.1 gm./kilo p.o. Total = 5.7	2850	25	48.8	2600	11.9	45.5	1650	4	22.5		T	T	2.9	51
E. P.	Single 0.1 gm./kilo p.o. Total = 6.8	1675	50	79	900	31.2	141.5	1000	4	16.8		T	T	2.34	39
J. B.	3.6 gm. per day p.o.	1440	30	155	1520	40.8	137	1350	53.6	166				6.55	60
H. W.	3.6 gm. per day p.o.	1840	62.5	105	1780	47	89.9	2640	40	77				5.52	51
D. J.	3.6 gm. per day p.o.	2130	36.4	107	2240	31.3	95.7	2310	38.1	111				6.97	64
W. B.	2.4 gm. per day p.o.	1410	24.9	131.5	1630	22.2	126	1120	20	114				5.16	86
W. B.	Single 3.46 gm. I.V.	1625	49.4	134	2915	29.1	108.2	1915	1.7	6.6	3450	1.2	2.3	2.52	72.6

U.V. = Urine volume. F = Free sulfapyridine. T = Total sulfapyridine (includes conjugated fraction).

the body of the drug. This is to be contrasted with the excretion of sulfanilamide which, under similar conditions, would be complete in about 72 hours. It is also of interest to note that from 39 to 79 per cent of the ingested drug was recovered from the urine in the four day period.

In the four patients who were convalescent from disease and to whom doses of the drug were being given at regular intervals, studies made over a period of three days showed that from 51 to 86 per cent of the ingested drug was being excreted in the urine. These figures are, in general, considerably lower than would be expected if sulfanilamide had been prescribed, and while we have not measured the amount of drug excreted in the stool, we believe the figures dealing with the excretion of sulfapyridine in the urine represent fairly accurate data as to the amount of the drug actually absorbed from the gastrointestinal tract.

Another factor of some consequence which is brought out in table 2 is that, as a rule, the percentage of *conjugated sulfapyridine* is quite high in the urine. This is, of course, of considerable importance when the question arises as to the use of the drug in certain types of urinary tract infections, because the conjugated form is known to be inactive. Then, too, the fact that acetylsulfapyridine is so poorly soluble tends to make it precipitate out in the urine of many patients. The crystals, which initially

are small, and boat or spear head-shaped, may coalesce and form calculi such as have already been reported as occurring in the urinary tract of animals and human beings.[5-7]

The difficulties which we had encountered in certain patients in either obtaining or maintaining a proper concentration of "free" sulfapyridine in the blood, led Dr. E. K. Marshall, Jr. and one of us [8] to try the therapeutic effects of the sodium salt of sulfapyridine by the intravenous route. As will be seen in table 1, the intravenous injection of 0.05 gram per kilogram of body weight promptly gave a blood level of slightly over 5 milligrams per cent. This level was moderately well maintained over a period of from six to eight hours. In table 2, data are given concerning the excretion of sulfapyridine over a period of four days following the injection of a single dose of sodium sulfapyridine. The observations which we have made concerning the absorption of sulfapyridine, its distribution through the body and its excretion have been substantiated by the reports of several other observers.[3, 9, 10]

The Clinical Use of Sulfapyridine in the Treatment of Pneumococcal Pneumonia

During the past year we have used sulfapyridine in the treatment of a wide variety of infectious diseases. As a result of our experience up to the present time, we feel justified in stating that sulfapyridine is superior to sulfanilamide in the treatment of pneumococcal, staphylococcal and possibly Friedländer's bacillus infections. In these infections the experimental and clinical evidence definitely favors the use of sulfapyridine. In other types of infection, reliable data are not as yet at hand.

There have been numerous reports [11-25] concerning the use of sulfapyridine in the treatment of pneumococcal pneumonia in children and adults. In their original communication, Evans and Gaisford [11] reported that they had treated with sulfapyridine 100 patients who were suffering from lobar pneumonia, and that in this group the case fatality rate was 8 per cent, this to be compared with a fatality rate of 27 per cent in a group of 100 patients who had received symptomatic treatment for lobar pneumonia. While the types of infecting pneumococci were not determined in the majority of these patients, and no data were reported as to the incidence of bacteremia, this communication of Evans and Gaisford is very significant of the therapeutic effects of sulfapyridine in lobar pneumonia. With the exception of this report in which adequate numbers of patients were discussed, many of the early communications, dealing with the use of the drug in pneumonia, were based upon individual cases or upon small groups of patients. However, in the issues of the *Journal of the American Medical Association* and *The Lancet* for February 11, 1939, Flippin and his associates [14] and Agranat et al.[15] described two large series of pneumonia patients who had been treated with sulfapyridine.

In the report of Flippin and his associates [14] the chemotherapeutic effects of the drug were studied in 100 patients ill with lobar pneumonia. In each instance a recognized type of pneumococcus was isolated from the sputum, and in 96 of the patients a blood culture was taken. A review of these cases shows that the distribution of the etiological types of pneumococci was not unusual, in that 83 per cent of the pneumonias were caused by organisms that belonged to the first eight types of pneumococci. However, the fact that the majority of the pneumonias were associated with types of pneumococci which produce the more severe forms of the disease was offset by two factors, the first being that the pneumonias occurred in the late summer, fall and early winter, while the second was that 60 per cent of their patients fell into the 39 year or under, age group. Eight of these hundred patients had positive blood cultures. Four patients succumbed to their infection. (Three patients whose disease terminated in death were excluded from this series because they died in less than 12 hours after treatment was started.) Despite the fact that the patients reported upon were in young age groups, that the bacteremic incidence was low and that the pneumonias were occurring during the fall and early winter, it seems certain to us, after reviewing this paper, that the drug was influencing favorably the course of lobar pneumonia.

It is more difficult to assess the results obtained by Agranat and his co-workers [15] in South Africa, because in many of the patients the type of infecting pneumococcus was not determined, blood cultures were not done, and a certain number of their treated and control patients had previously been inoculated with a pneumococcal vaccine. It was noted that in native miners the case fatality rates on the treated and untreated groups showed no significant difference, while in non-mining pneumonia patients, both colored and European, those who were treated with sulfapyridine showed a marked reduction in the case fatality rate as compared with the control group. In all of the treated groups the course of the pneumonia seemed to be altered in that the average rate of the return of the temperature to normal was accelerated as compared to the control groups, and despite the lack of certain essential data, the conclusion that sulfapyridine was "a valuable drug for the effective treatment of pneumonia both in Europeans and in natives" seems to be justified.

Duncan Graham and his associates [20] have reported a carefully studied series of patients ill with pneumococcal pneumonia and treated with sulfapyridine. Every effort was made by these observers to establish the etiological agent in the pneumonias. A perusal of their data shows an essentially normal distribution of the types of pneumococci, an age group distribution which favors the severity of the disease, a bacteremic rate which was high (34 per cent) and (at least in the early part of their studies) an untreated control group of 30 patients in which the case fatality rate was 23.3 per cent. As a result of therapy with sulfapyridine the case fatality rate in the treated group of 50 patients was reduced to 6 per cent

and in the 17 patients who had a bacteremia only three, or 17.6 per cent, died. These results were certainly striking.

In their original communication Evans and Gaisford [11] referred briefly to the apparently successful use of sulfapyridine in the treatment of pneumonia in children. Barnett and his associates [16] have reported that the drug gave good results in the therapy of pneumococcal pneumonias in infants and children. They advocate its prompt use in pneumonia, particularly if the pneumonia is suspected of being caused by the pneumococcus.

Hodes and his associates [19] have described their experience with the drug in 71 infants and children who were ill with pneumococcal pneumonia. In 33 of the patients the disease was primary, while in 38 the pneumonia was associated with measles. In all instances pneumococci, identified by type-specific sera, were obtained from the rhinopharynx, and consolidation of the lungs was shown by roentgenograms. In the group of primary pneumonias type 14 seemed to be the most common organism, and in the pneumonias associated with measles, type 14 was also commonly found as the etiological agent. Composite average temperature charts of these two groups of patients showed that the temperature reached normal in 40 hours after the beginning of treatment in the group of primary pneumonias, and in 30 hours in the group of pneumonias which was associated with measles. None of the 71 patients died. It was our privilege to see a number of the patients included in this series, and it was often striking to note the immediate marked clinical improvement which followed the institution of sulfapyridine therapy.

Our own experience with the use of sulfapyridine dates from July 1938, when, following preliminary laboratory observations upon the efficacy of the drug in the control of experimental pneumococcal infections in mice, its toxicity in animals and its rate of absorption and excretion in animals and human beings, we decided that our findings warranted careful clinical trials of the drug in pneumococcal pneumonia.

For more than 15 years, it has been the practice in The Johns Hopkins Hospital to employ specific pneumococcal antisera in the treatment of pneumococcal pneumonia. The results obtained over a period of years from the use of specific antisera in types I and II pneumococcal lobar pneumonia were very satisfactory, and during the past three years, following the introduction of specific horse and rabbit antisera, not only for types I and II, but also for type III and the higher types IV to VIII and XIV, we have been able to increase the number of patients who received the benefits of serum therapy in the course of lobar pneumonia.

During the past three years when sera of high potency for types I to VIII and XIV have been available, and especially since we have controlled the administration of antipneumococcal serum with the specific capsular polysaccharide skin test, our results in the therapy of pneumococcal pneumonia have been excellent. Therefore, at the beginning of our clinical studies with sulfapyridine, we did not feel that enough evidence was at hand to

justify the abandonment of serum in favor of the drug. We accordingly decided to use specific antiserum in those cases for which it was available and to give sulfapyridine to patients ill with pneumococcal pneumonia, for the treatment of which serum was not available and to those in whom the use of serum was contraindicated because of a history of asthma or hypersensitivity to serum. This plan was adhered to until early in February 1939, at which time, due partly to the excellent results already obtained from the peroral use of sulfapyridine in patients ill with lobar pneumonia, and partly to the fact that the use of sodium sulfapyridine by the intravenous route had been demonstrated to be entirely feasible, we decided to discontinue the primary use of specific pneumococcal antisera and to depend upon sulfapyridine and sodium sulfapyridine for the treatment of patients ill with lobar pneumonia.

It has for many years, been the custom at The Johns Hopkins Hospital to make every effort to type pneumococci isolated from the sputum, blood or exudates of patients ill with lobar pneumonia. The mouse-inoculation test, Avery tube method and the usual cultural methods of isolating pneumococci were used. When pneumococci were isolated, typing by macroscopic agglutination tests was always attempted. More recently the "Quellung" reaction of Neufeld has been added to these procedures. Thus, the patients described in this study have not only had the usual physical and roentgenographic examinations, but also very careful bacteriological studies in an attempt to identify the etiological agent of their pneumonias. If pneumococci were found in the cultures or in the exudate from the mouse peritoneum, attempts were always made to type the organisms either as a check on the Neufeld reaction in the sputum or as a primary diagnostic measure. In those patients in whom it was difficult to obtain sputum, an effort was made to isolate and identify pneumococci in cultures from the rhinopharynx. Cultures of the patient's blood have been made at frequent intervals and if positive, the type of pneumococci was determined. The same has been done with all exudates which have been obtained from patients ill with lobar pneumonia. In certain patients, from whom sputum was not obtained, the identification of the etiological agent of their infection was accomplished by means of lung punctures, and in one instance the type of the pneumococcus was determined by identifying the soluble specific pneumococcal capsular polysaccharide in the urine of the patient by means of precipitin tests. We have not been able to confirm the observation of Telling and Oliver [12] that sulfapyridine therapy alters the capsule of the pneumococcus, thus making the typing of pneumococci difficult after treatment with the drug has been started. It may seem that we have stressed unduly our efforts at typing pneumococci, but we feel that we have been justified in doing so, and that *every effort should be made in the future, when facilities are available, to determine the type of pneumococcus that is responsible for a given case of lobar pneumonia.* It is only by following

such a practice that a real knowledge of the effectiveness of sulfapyridine may be obtained.

From July 1, 1938 until June 20, 1939, 139 adult patients (i.e., over 15 years of age) were treated in The Johns Hopkins Hospital for presumptive pneumococcal pneumonia. As is shown in table 3, pneumococci, identified by specific antisera, were obtained from the sputa of 124 of these patients, in five individuals pneumococci were identified in the sputum but it was not possible to type the organisms, and from 10 patients pneumococci were not isolated at any time during the course of their disease.

TABLE III

The Course of Pneumococcal Pneumonia in Adult Patients in the Johns Hopkins Hospital from July 1, 1938 to June 20, 1939

Type	No. of Cases	Bacteremic Incidence on Admission	No. Cases Treated with			Incidence of Complications	Incidence of Concurrent Disease	Case Fatality Rate
			serum	sulfapyridine	serum and sulfapyridine			
1	24	6	13	11		2	5	1
2	6	4	1	3	2	4		1
3	20*	1	4	13	3	1	10	2
4	10	1	4	6			5	1
5	5	1	1	3	1	1	3	1
6	1			1			1	
7	11	3	5	6		4		
8	14	3	3	10	1	1	8	1
11	2			2				
12	1			1				
13	1	1		1		1		1
14	3			3		1		
15	1	1		1				
16	2	1		1	1	1		
17	1			1			1	
18	4			4			1	
19	6	1		6		1	2	1
20	4			4		1	2	
22	2			2			2	
23	1			1			1	
24	1			1			1	
25	2			2			1	
32	2			2			2	
Untyped	15			15			6	1
Total 1938–39	139	23 or 16.5%	31 or 22.3%	100 or 72%	8 or 5.7%	18 or 13.7%	51 or 36.6%	10 or 7.2%

* In this group, two patients had more than one type of pneumococcus isolated from their sputum.

On admission to the hospital 23 of the patients were found to be suffering from a pneumococcal bacteremia. Thirty-one of the patients were treated with type specific pneumococcal antisera, 100 patients with sulfapyridine, and eight were treated with type specific serum and sulfapyridine. Eighteen of these patients suffered from a complication resulting from the infection, while 51 had major concurrent diseases which are recognized as

unfavorably influencing the course of pneumonia. Ten of the 139 patients died, thus giving a *case fatality rate of 7.2 per cent.* This case fatality rate is probably the lowest for pneumococcal pneumonia in the history of The Johns Hopkins Hospital.

It is obvious in assessing the results of any type of therapy, that adequate controls should, when possible, be presented. This we are unable to do, but we believe that a review of the course of pneumococcal pneumonia during the past four years in this hospital, will attest the validity of our figures. This is especially necessary in view of the often repeated statement that pneumonia has not been as severe as usual during the past year.

Our data present four possible criteria by which we may judge the validity of our experience during the past year. It is important to know whether the type distribution of pneumococci (as determined by the incidence of types I, II and III pneumonias) was similar to that of previous years, whether the incidence of bacteremia was comparable, whether any shift in the age distribution of the patients had taken place, and whether the occurrence of major concurrent disease was the same as in past years. In the latter category we place heart disease of various types, diabetes, asthma, tuberculosis, chronic alcoholism, pregnancy, and surgical procedures, all of which are known to influence unfavorably the course of lobar pneumonia.

TABLE IV

The Course of Pneumococcal Pneumonia in Adult Patients in the Johns Hopkins Hospital from July 1, 1935 to June 20, 1939

Year	No. Cases	Bacteremic Incidence		No. Cases Treated			Incidence of Complications	Incidence of Concurrent Disease	Case Fatality Rate
		Admission	Late	Specific Serum	Sulfapyridine	Serum and Sulfapyridine			
1935–1936	157	21 or 13.3%	2 or 1.2%	31 or 19.7%			33 or 21%	31 or 19.7%	30 or 19.1%
		23 or 14.5%							
1936–1937	181	28 or 15.5%	7 or 3.8%	46 or 25.4%			27 or 14.8%	64 or 35.3%	38 or 21%
		35 or 19.3%							
1937–1938	148	20 or 13.5%	4 or 3%	61 or 40.1%			20 or 13.5%	62 or 40.2%	26 or 17.6%
		24 or 16.5%							
1938–1939	139	23 or 16.5%		31 or 22.3%	100 or 72%	8 or 5.7%	18 or 13.7%	51 or 36.6%	10 or 7.2%

In table 4 is outlined the course of pneumococcal pneumonia in adult patients in this hospital from July 1, 1935 until June 20, 1939. While the data are not included in table 4, we may state that the incidence of types I, II and III pneumococcal pneumonias was 35.6 per cent, 32.5 per cent, 33.7 per cent and 35.9 per cent per year from 1935 to 1939. Hence, our

record of this year is not dependent upon a shift in the type distribution of pneumococci.

The incidence of bacteremia as shown in table 4 is of considerable interest and importance. It is noteworthy that during the past year 16.5 per cent of the patients who were ill with pneumonia had a positive blood culture at the time of their *admission* to the hospital, and that *none* of the patients whose blood cultures were negative upon entrance to the hospital subsequently developed a positive blood culture. This is in contradistinction to each of the previous years during which a certain number of patients ill with pneumonia entered the hospital without bacteremia and subsequently developed it. Hence, while the total bacteremia rate is slightly lower this year than in the previous two years, the rate on *admission* is the highest of the last four years.

We have determined the prognostic importance of the presence of bacteremia upon the course of pneumonia during the past four years. In table 5 are data which bear upon this point. It is to be noted that 30 out

TABLE V

The Case Fatality Rates in Untreated and Treated Adult Patients Ill with Bacteremic Pneumococcal Pneumonia in the Johns Hopkins Hospital from July 1, 1935 to June 20, 1939

Type	Untreated	Deaths	Serum Treated	Deaths	Sulfapyridine Treated	Deaths	Serum and Sulfapyridine Treated	Deaths
1	1	1	28	10	3			
2	1	1	3	2	1		2	1
3	8	8	3	2				
4					1	1		
5	3	2	1	1			1	1
7	1		7	2				
8	4	3	4	1	3			
10	4	3						
12			1					
13					1	1		
14			2	1				
15					1			
16					1			
19					1	1		
20	1							
25	1	1						
Group IV	14	11						
Total	38	30 or 80%	49	19 or 38%	12	3 or 25%	3	2 or 66%

of 38 untreated patients ill with pneumonia and in whom the presence of bacteremia had been determined, succumbed to their disease. A review of the eight patients who survived shows that with one exception the colony count of pneumococci was below one per cubic centimeter of blood, the exception showing three colonies per cubic centimeter. Also, with one exception, only a single blood culture was positive for pneumococci. These

figures are in accord with the general opinion that the presence of bacteremia is of extremely bad prognostic significance in the course of pneumococcal pneumonia in adult patients.

The age of the patient has a definite bearing upon the course and severity of pneumococcal pneumonia. The prognosis in this disease becomes less favorable as the age of the adult patient increases. Hence, it is of importance in evaluating our results during the past year to make certain that there has not been a significant shift in the age distribution of the treated patients. In table 6 is shown the percentage of patients in various age groups. It is clear that there has not been any significant change in the age-distribution of our pneumonia patients during the past year.

TABLE VI

Age Incidence of Adult Patients Ill with Pneumococcal Pneumonia in the Johns Hopkins Hospital from July 1, 1935 to June 20, 1939

Year	15–19 years	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years	80–89 years
1935–36	9.3%	29.7%	28.2%	15.4%	10.3%	3.8%	2.6%	0.7%
1936–37	8.4%	24.3%	26.0%	16.4%	11.9%	7.9%	4.0%	1.1%
1937–38	14.2%	22.9%	17.2%	22.0%	11.9%	8.6%	2.4%	0.8%
1938–39	5.1%	22.0%	28.8%	20.3%	8.5%	11.0%	4.3%	0.0%

If a patient ill with pneumonia is suffering from one or more other major diseases, his chances of recovering are impaired. The same holds true for pregnant women and for patients who have undergone a recent major surgical operation. As is shown in table 4, the incidence of concurrent disease during the past year did not vary markedly from that reported during the previous three years.

We feel justified, therefore, on the basis of the data which we have just presented, in concluding that the pneumonias which we have seen in adult patients in The Johns Hopkins Hospital during the past year were as severe as those observed during the period from 1935 to 1938. It is logical, therefore, to attribute the marked decline in the case fatality rate in pneumococcal pneumonia noted during the past year to improvements in our treatment of pneumonia, rather than to the vagaries of chance, or to a sudden decline in the "virulence" of the pneumococcus.

During the past year we treated 31 patients suffering from lobar pneumonia with type specific pneumococcal antisera. These and certain other patients so treated will be included in a separate report by Dr. W. Barry Wood, Jr. In this same period of time 100 patients have been treated with sulfapyridine and eight have been treated with sulfapyridine in combination with type specific antiserum.

The course of pneumonia in those patients who were treated with sulfapyridine is outlined in table 7. It is to be noted that 56 per cent of this group of patients would ordinarily have been treated with type specific sera

TABLE VII

The Course of Pneumonia in Patients Treated with Sulfapyridine

Type	No. of Cases	Bacteremia		Incidence of Complications	Incidence of Concurrent Disease	Toxic Reactions	Case Fatalities
		Co./c.c.	No.				
1	11	36/c.c. ++	3	Pleural Effusion 1	4	1	
2	3	4/c.c.	1	Pleural Effusion 2	1		
3	13				7	1	
4	6	+	1		3	1	1
5	3				3		
6	1				1	1	
7	6					1	
8	10	+++	3	Empyema 1	5		
11	2						
12	1						
13	1	+	1	Empyema 1			1
14	3				1		
15	1	+	1			1	
16	1	21/c.c.	1		2		
17	1				1		
18	4				1		
19	6	6/c.c.	1	Pleural Effusion 1	3		1
20	4				1		
22	2				2		
23	1				1		
24	1						
25	2						
32	2						
Untyped	5				2	1	1
No. Pneu.	10				5		
Total	100		12	5	42	7	4

of types I to VIII, or XIV. Twelve per cent of these hundred patients had positive blood cultures, and five developed a complication associated with their pneumonia. Forty-two per cent of the patients had major concurrent diseases, while seven suffered from severe toxic reactions due to drug therapy other than those of nausea and vomiting. Three of the patients died, one 45 minutes after the first dose of sulfapyridine, a second six hours after the initial administration of the drug and the third (who probably had bilateral empyema when treatment was started) on the third day of therapy.

The clinical response of these patients to sulfapyridine therapy was, as a rule, quite prompt, and this was especially true when blood concentrations of free sulfapyridine of 4 milligrams per cent or more were reached within the first 24 hours of treatment. The clinical course of pneumonia associated with bacteremia and the response of the disease to sulfapyridine therapy is shown in the temperature records of four patients which are portrayed in chart 2. As will be noted, in each case shown in this chart, the concentration of free sulfapyridine in the blood was 4 milligrams per cent or more within the first 24 hours of treatment.

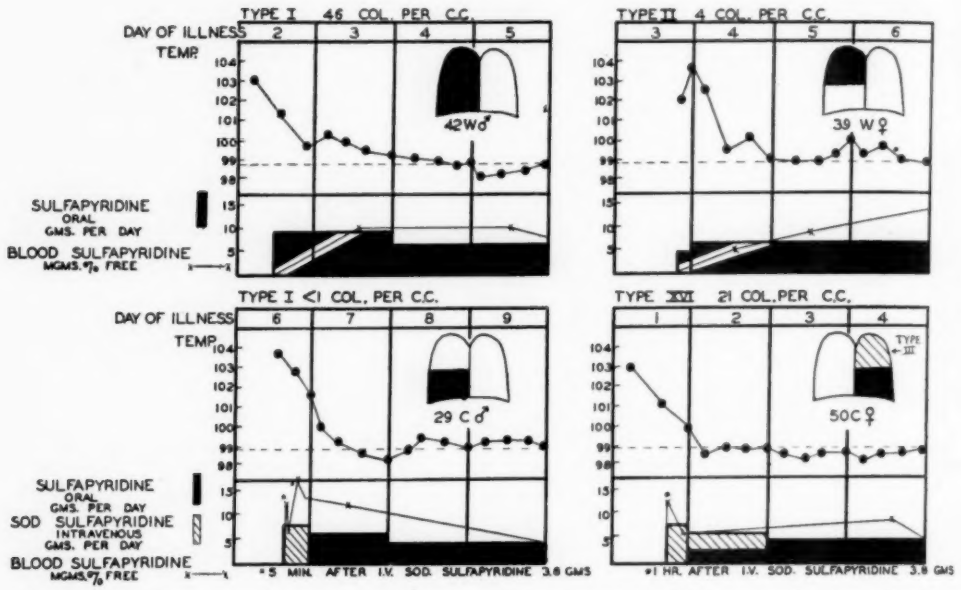

CHART II. Representative cases of pneumococcic pneumonia with bacteremia treated with sulfapyridine and sodium sulfapyridine.

It has been our practice to continue therapy with sulfapyridine until the patient is completely convalescent, and the signs of the disease have disappeared. The response to the drug is frequently very dramatic, and one may be tempted to discontinue sulfapyridine, especially if nausea and vomiting are present as a distressing side effect of the drug. Such a procedure generally results in a recurrence of the disease. Chart 3 shows two such instances.

The first patient was an elderly woman who because of nausea and vomiting refused sulfapyridine after 36 hours of treatment. Although the temperature was normal at the time the drug was discontinued, a secondary rise occurred 40 hours after sulfapyridine had been stopped. Treatment with the drug was resumed, the temperature quickly returned to normal, nausea and vomiting recurred, and the patient again refused to take any more sulfapyridine. As will be noted, a rise in temperature accompanied by a spread in the pneumonic process occurred within 24 hours. Further treatment with sulfapyridine was not attempted and the patient eventually recovered.

The second patient represents an individual in whom the dose of sulfapyridine was decreased too rapidly. On the fifth day of his disease, when the temperature spiked upwards, it was thought that the fever was a toxic manifestation of the drug and sulfapyridine was discontinued for 24 hours. At this point the patient's blood culture was negative. The concentration of the drug in the blood fell practically to zero in the 24 hours after the drug was stopped. On the sixth day it became clear that the febrile reaction

was due to the development of an empyema. Despite intensive oral sulfapyridine therapy, the blood cultures became positive again, the course of the empyema was unchanged, and a closed drainage eventually had to be performed.

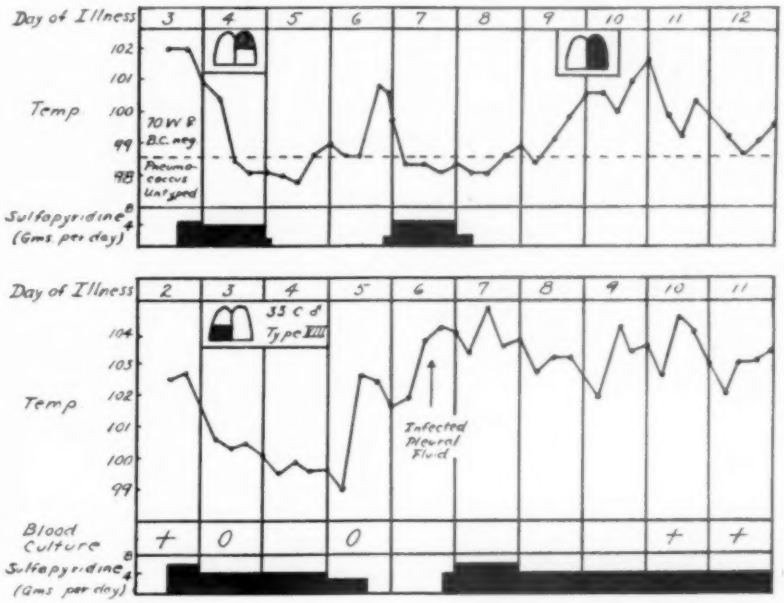

CHART III. Relapse of pneumococcic pneumonia due to inadequate treatment with sulfapyridine.

The evolution of the clinical course of pneumonia in patients who are treated with sulfapyridine varies considerably. In patients who receive adequate therapy and in whom effective concentrations of the drug in the blood are rapidly obtained, the temperature generally returns to normal within 18 to 48 hours after the beginning of treatment. The elevated pulse rate, as a rule, is slower in returning to its normal value. The respiratory rate generally decreases as the temperature recedes, but in certain instances, (especially if the pneumonia is extensive) the respirations may be rapid for 24 to 48 hours after the temperature has been normal.

There are marked and unpredictable variations in the evolution of the physical signs of pneumonia in patients who are treated with sulfapyridine. The existing signs of consolidation may disappear with great rapidity as the temperature comes to normal or as we have frequently noted, these signs may become much more marked over a period of several days after the fever has disappeared. It has seemed to us in many instances that the drug, while bringing about a marked betterment in the general well-being of the patient, has not altered the usual evolution of the pneumonic process in the lungs. We have not observed that therapy with sulfapyridine prolongs the course of resolution of pneumonic processes. It is important,

therefore, as we have already shown in chart 2, to continue the drug until signs of resolution are complete, if relapses of the disease are to be avoided.

Eight patients have been treated with sulfapyridine in combination with type specific pneumococcal antiserum during the past year. Two of these patients were ill with type III pneumonias, and because their response to drug therapy was slow, they were given specific antiserum which brought about a prompt recovery. One patient entered the hospital ill with a type VIII pneumonia and meningitis and died after eight hours of combined therapy. A fourth patient who had been treated with type V antiserum, had an acute bacterial endocarditis which was fatal in spite of sulfapyridine therapy. A fifth patient received sulfapyridine after an intravenous injection of serum had precipitated a moderate anaphylactic attack. A sixth patient ill with a mixed type III and X pneumonia was treated with type III specific antiserum and sulfapyridine. Two patients received adequate treatment with sulfapyridine both by the oral and intravenous routes without bringing their disease under control, and because of their lack of response to the drug were finally treated with specific pneumococcal antisera. These patients are of special interest because they represent definite failures of sulfapyridine therapy.

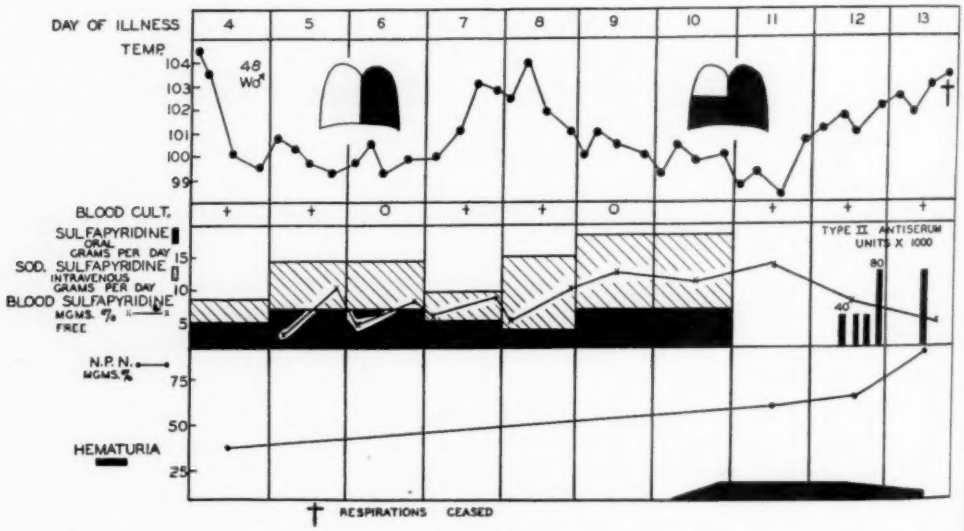

CHART IV. Case of type II pneumonia which failed to respond to intensive treatment with sulfapyridine.

The course of the first of these patients is outlined in chart 4. This man entered the hospital on the fourth day of a type II pneumonia, with involvement of the entire left lung. He seemed quite ill and intensive therapy with sulfapyridine by the oral and intravenous routes was begun. The initial blood culture showed type II pneumococci. It seemed as though the patient was making a good response to treatment during the first 48

hours, but then, despite intensive therapy and the maintenance of an adequate concentration of the drug in the blood, the disease progressed. On the tenth day hematuria developed and the drug was stopped. Within 24 hours the temperature began to rise, the hematuria increased, the urine volume decreased, the non-protein-nitrogen was found to be elevated, and the patient became critically ill. Specific serum therapy was instituted, but it was unsuccessful and the patient died. At autopsy acetylsulfapyridine calculi were found in both kidney pelves.

This experience made us realize that we could not rely upon sulfapyridine therapy in every instance, and that we would encounter certain patients in whom intensive therapy with the drug would be to no avail. The course of another such patient is shown in chart 5. This patient, a 40

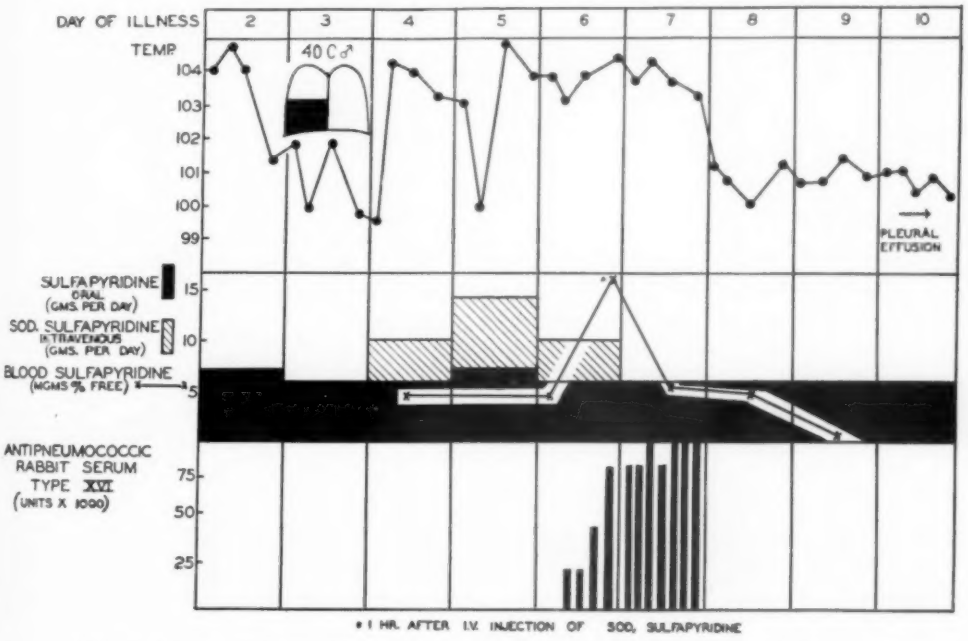

CHART V. Case of type XVI pneumonia which failed to respond to treatment with sulfapyridine.

year old colored man, entered the ward on the second day of a type XVI pneumonia with one lobe involved by the pneumonic process. The blood culture was negative and remained so throughout the course of his disease. Oral therapy with sulfapyridine was started and during the first 48 hours it seemed as though he was making a fair response to the drug. On the fourth day the temperature became sharply elevated, and treatment by the intravenous route was begun. Despite intensive therapy, the disease process was not brought under control, and on the sixth day serum therapy was started. A total of 760,000 units of type XVI antipneumococcal rabbit serum was required to induce a partial crisis in this patient. Even so, the

temperature did not come down to normal and the patient eventually developed a sterile pleural effusion.

The histories of these two patients are of the greatest importance because they indicate that therapy with sulfapyridine will not give satisfactory results in all patients ill with pneumococcal pneumonia, and that the physician must be prepared to administer type specific antipneumococcal serum in such instances. We are uncertain as to how long one should rely upon sulfapyridine therapy in a given patient who does not seem to be responding promptly to treatment. Our impression at present is that if intensive sulfapyridine therapy with the immediate attainment and maintenance of concentrations of 4 milligrams per cent or more of the drug in the patient's blood does not result in a marked improvement in his condition within 48 hours, therapy with type specific antipneumococcal serum is indicated.

The problem of whether treatment with type specific antisera combined with adequate doses of sulfapyridine might not be the best method of therapy for pneumococcal pneumonia, has not been settled. We can see no objection, except that of the cost of serum, to such a procedure and there are theoretical considerations which indicate that combined therapy might be the ideal method of treatment. Certainly, if faced with a severe pneumococcal pneumonia due to a type of pneumococcus for which a potent serum was available, we would not hesitate to use serum and sulfapyridine.

It has been said that the "day of serum therapy" in pneumonia is limited because of the introduction of sulfapyridine as a therapeutic agent in this disease. This we believe to be a careless over-statement. We have already shown that certain cases of pneumonia may prove to be resistant to treatment with the drug, and there are certain considerations which lead us to believe that in severe cases of pneumonia, combined serum and sulfapyridine therapy may be the best method of treatment. Then, too, as time goes on, it will be found that an increasing number of people will be intolerant to sulfapyridine, and if such individuals develop pneumonia, treatment with serum will be the only specific method of therapy that will be possible.

In the summer and fall of 1938 it was our practice to administer 1.0 gram (15 grains) of the drug every four or six hours. However, as our studies progressed, it became evident that if the infection was to be brought under control rapidly, an initial dose of 4.0 grams of the drug followed by 1.0 gram every four hours offered the best chance of rapidly combatting the infection. At the present time our system of dosage for adult patients who are moderately ill with lobar pneumonia is as follows:

1. 4.0 grams *stat.* as soon as the clinical diagnosis of pneumonia is established.
2. Then, 1.0 gram every four hours (day and night) until the temperature has been normal for 48 hours.
3. Then, 1.0 gram every six hours until resolution is well under way.

4. Finally, 0.5 gram four times a day until the patient is ready to leave his bed.

If, however, on the day after treatment with sulfapyridine has been started, the rectal temperature of the patient is not below 101° F. and the concentration of "free" sulfapyridine in his blood is under 4 milligrams per cent, it is our practice to give the patient one dose of 0.06 gram per kilogram of body weight of monohydrate sodium sulfapyridine by the intravenous route. The peroral administration of the drug is continued as before.

In preparing sodium sulfapyridine for intravenous use the required amount of the drug is weighed out and dissolved in enough *sterile, distilled* water to make a *5 per cent solution.* Sodium sulfapyridine is unstable to heat and, hence, such solutions cannot be sterilized. However, since a 5 per cent solution of sodium sulfapyridine has a pH of 10.7 to 10.8, it is, in itself, somewhat bactericidal. The drug is *always administered by the intravenous route,* and great care must be taken to be sure that the needle is well in the vein before the injection is started in order to avoid getting any of the solution into the tissues. As with alkalinized arsphenamine, the injection of the sodium salt into the tissue results in a painful area of induration which may eventually slough. With the needle in the vein, the solution is injected slowly, 1 minute being required for the injection of 5 cubic centimeters, thus making the time of injection from 10 to 15 minutes in the average adult.

In pneumonia patients who are seriously ill we prefer to start treatment by the intravenous injection of solutions of sodium sulfapyridine in order that adequate concentrations of the drug may be quickly obtained. Hence, we generally give an initial dose of the monohydrate sodium salt based upon 0.06 gram per kilogram of body weight and repeat this dose in from four to six hours. Such a dose will produce a blood concentration of about 5 milligrams per cent of the drug within a few minutes after it is injected. At the same time we begin peroral medication using 1.0 gram of sulfapyridine every four hours. This type of combined peroral and intravenous therapy permits one to obtain and maintain adequate concentrations of the drug in the blood of patients who are seriously ill. In our experience we have rarely had to use more than two intravenous injections of the drug and have found that after the first few hours it is safe to rely upon peroral medication alone. It is to be remembered that within a very short time after a solution of the sodium salt is injected, the sodium ion is probably split off and the substance circulating in the blood is sulfapyridine.

It is often difficult to obtain and maintain effective blood concentrations of sulfapyridine in patients because of the nausea and vomiting caused by the drug. In these individuals the intravenous use of sodium sulfapyridine is advantageous. Sodium sulfapyridine is also a valuable adjunct in the treatment of pneumococcal infections in patients whose tissues conjugate the drug to a high degree. In such instances the judicious use of

sodium sulfapyridine makes it possible to maintain adequate concentrations of the drug. It must be remembered, however, that the tissues will conjugate sulfapyridine which is given by the intravenous route in the same manner as that given *per os*. Sodium sulfapyridine is also of value in the treatment of patients in whom, because of recent surgical procedures, the peroral use of the drug is undesirable. In all instances, however, it must be kept in mind that following the intravenous use of sodium sulfapyridine, the patient is just as likely to suffer from nausea and vomiting as he is when the drug is given by mouth. There is little reason to believe that the intravenous use of the drug lessens the incidence of nausea and vomiting.

The auxiliary treatment of patients who are ill with pneumococcal pneumonia and who are being treated with sulfapyridine should be essentially the same as that used before the drug was available. *Fluids should not be limited nor should they be forced to extremes.* Our observations lead us to believe that a fluid intake of 3500 cubic centimeters a day is adequate during the first days of treatment, and we force and limit fluids to this level. The diet may be as desired. As far as our experience goes, we have not found that sulfapyridine was incompatible with other drugs and we never hesitate to use them if they are indicated by the needs of the patient. We have not used saline laxatives or cathartics.

In the beginning of our use of sulfapyridine we noted that therapy with the drug was not accompanied by a drop in the CO_2 combining power of the blood and, hence, we thought it unnecessary to use bicarbonate of soda. Recently, however, we have been administering bicarbonate of soda gram for gram with sulfapyridine with the idea of rendering the urine so alkaline (pH 7.5) that the precipitation of acetylsulfapyridine would be hindered. While theoretical conditions indicate that this might be a valuable procedure, enough factual evidence is not at hand to assess the real value of this type of therapy.

The Effect of Sulfapyridine Therapy upon the Complications of Pneumococcal Pneumonia

While the incidence of serious complications has been low in the series of cases which we have just discussed, we are of the opinion that the number of patients observed by us is too small to form a basis for any judgment as to the possible effects of sulfapyridine therapy upon the incidence of complications in the course of pneumococcal pneumonia.

We have tested the therapeutic effects of the drug in three infected empyemas during the past year and in each instance a closed drainage of the empyema eventually had to be done. In one patient suffering from an acute pneumococcal endocarditis, therapy with sulfapyridine was unsuccessful and the patient died. This group of patients is obviously too small to be of much value in assessing this phase of sulfapyridine therapy.

The Toxic Manifestations of Sulfapyridine Therapy

Sulfapyridine produces many of the toxic manifestations which have previously been described in the course of sulfanilamide therapy. It is our impression, based upon the observation of the patients included in this report and upon about 400 other individuals who were ill with miscellaneous infections and treated with sulfapyridine during the past year, that the toxic manifestations of this drug are, with two exceptions, somewhat less common than those of sulfanilamide. Sulfapyridine causes definitely more nausea and vomiting than does sulfanilamide and is known (in its conjugated form) to be responsible for the formation of renal calculi. It is important to remember that if a patient has once had a toxic reaction in the course of sulfanilamide or sulfapyridine therapy, a second and more severe one may occur, if one or the other of these drugs is administered a second time.

Central Nervous System Effects. The most common toxic manifestation of sulfapyridine therapy is nausea and vomiting. This is more common in adults than in children, and occurs more frequently in white patients than it does in negroes. It is frequently quite severe and often renders peroral therapy with the drug difficult. In the series of cases which we have just reported there was but one patient in whom vomiting was so severe that it was thought best to discontinue the drug. It was believed during the early use of sulfapyridine therapy that the nausea and vomiting were the results of gastric irritation produced by the drug. The observations of Marshall and Long[8] have definitely disproved this hypothesis and show that the vomiting is the result of an action of the drug upon the central nervous system. For this reason the use of demulcents is not indicated in the course of sulfapyridine therapy.

The drug may cause a mild depression in certain individuals, and on two occasions we have encountered patients who suffered from toxic excitement in the course of sulfapyridine therapy. Early in the course of our use of the drug, Dr. James Bordley III pointed out to us that, in addition to a mild depression, certain patients spoke in a slow monotone, had waxy, deliberate movements, thus resembling individuals suffering from a mild attack of encephalitis. This syndrome may persist for several days after the drug has been stopped. We have noted no instance of a toxic peripheral neuritis in the course of therapy with sulfapyridine.

Dermatitis. We have seen several instances of measly eruptions very similar to those occurring in the course of sulfanilamide therapy, in patients who were receiving sulfapyridine. Individuals who are receiving sulfapyridine should keep away from sunlight. In patients developing a rash we have always discontinued the drug.

Fever. Drug fever, similar to that described in the course of sulfanilamide therapy, has been noted in several of our patients who were receiving sulfapyridine. In one instance a patient who had developed drug fever

in the course of sulfapyridine therapy, was noted to have the same toxic manifestation three weeks later when a course of sulfanilamide was instituted. This suggests that a patient who has had a severe toxic reaction to one of this group of drugs may develop the same toxic manifestation when another drug of the same group is prescribed.

Cyanosis. While cyanosis has been observed in our patients, it has occurred less frequently and with a lesser degree of intensity than has been our experience in the course of sulfanilamide therapy. We have not seen any deleterious effects resulting from the administration of the drug to patients who were ill with pneumonia and already suffering from cyanosis. Barnett and his associates [16] have reported that the cyanosis is due to formation of methemoglobin.

Acidosis. As far as we know, sulfapyridine does not produce acidosis.

Renal Irritation. Antopol and Robinson [5] have reported that they found acetylsulfapyridine uroliths in the urinary tracts of rats, rabbits and monkeys who had been fed large amounts of sulfapyridine. Gross and his associates [6] independently observed the formation of similar concretions in rats. Lawrence [26] suggested that the formation of acetylsulfapyridine stones might have been responsible for an attack of pain, followed by hematuria, which he noted in a patient who was receiving sulfapyridine. Southworth and Cooke [27] have described three patients in whom the administration of sulfapyridine led to hematuria accompanied, in two instances, by renal pain and nitrogen retention.

We have observed several patients who developed hematuria in the course of sulfapyridine therapy. One of these is of special interest. The clinical course of this patient, who was ill with type II pneumonia, and sulfapyridine, has already been portrayed in chart 3. It is to be noted that gross hematuria was first observed on the sixth day of treatment. The drug was immediately discontinued. On the next day the hematuria persisted and numerous boat and spearhead-shaped, brownish crystals were noted in the urine. The amount of urine excreted by the patient began to decrease and it was found that the non-protein-nitrogen of the blood was elevated. Over the next 36 hours the degree of hematuria decreased but the blood non-protein-nitrogen gradually increased until the death of the patient.

At autopsy, literally hundreds of small brownish renal calculi were found in both kidney pelves and ureters. These calculi were analysed by Dr. A. C. Bratton of the Department of Pharmacology and were found to contain 0.6 per cent sulfapyridine and 85.6 per cent of acetylsulfapyridine. The melting point of the material found in the stones was 226.8° to 227.8° C. after two recrystallizations from 6 N acetic acid. It was also observed that the melting point was unchanged by the addition of authentic acetylsulfapyridine. Hence, it seemed beyond doubt that these stones were made up mainly of acetylsulfapyridine. Studies of the histological sections of

the kidneys and ureters of this patient did not show abnormalities which could be attributed to stone formation.

Following this observation we have been watching the urine of patients receiving sulfapyridine for the occurrence of acetylsulfapyridine crystals. We have noted that practically all individuals who received the drug had acetylsulfapyridine crystals in their urine. We have been unable to correlate the number of crystals in the urine with the appearance of hematuria. In several patients, despite the presence of great numbers of acetylsulfapyridine crystals in the urine, hematuria, either microscopic or macroscopic, was not detected.

The question of when to stop sulfapyridine therapy in the presence of hematuria has not been settled. We have not discontinued the drug when 10 to 20 red blood cells per high power field appeared in the urine, if the clinical condition of the patients indicated that the drug should be continued. We do believe, however, that macroscopic hematuria is an indication that the drug should be stopped. Acetylsulfapyridine is soluble in alkaline solutions. This suggested the possibility of keeping the urine alkaline (pH 7.5) so that the tendency of acetylsulfapyridine to crystallize out would be diminished. Recently, we have administered bicarbonate of soda to patients who were receiving sulfapyridine. Our experience in this respect is not yet great enough to warrant any statement as to the value of the procedure.

Sulfapyridine and acetylsulfapyridine are excreted slowly, if the kidney function is diminished, and care should be taken in patients suffering from renal disease, that the drug does not accumulate in the body. We have administered sulfapyridine to patients who have grave impairment of renal function and did not note that the drug increased the degree of existing renal damage.

Hepatitis. We have observed one instance of hepatitis associated with jaundice and unaccompanied by acute hemolytic anemia, in a patient who was receiving sulfapyridine.

Disturbances in the Red Blood Cells. Two instances of acute hemolytic anemia occurring within the first five days of treatment have been noted in negroes who were receiving sulfapyridine. Slowly developing anemias seem to be somewhat less common in the course of sulfapyridine therapy than has been noted when sulfanilamide has been prescribed.

Disturbances in the White Blood Cells. We have observed two patients who developed agranulocytosis in the third week of therapy with sulfapyridine. The drug was immediately discontinued in both instances. One patient recovered from this toxic manifestation, and the other died. One patient, in the series of cases reported in this paper, developed a severe leukopenia at the end of the first week of treatment with sulfapyridine. The drug was stopped and the white blood cell count rapidly returned to normal.

Comment

The results which we have obtained during the past year from the use of sulfapyridine therapy in pneumococcal pneumonia are confirmatory of the findings of other observers, and support the belief that the drug is of great value in the treatment of pneumococcal infections. Our observations indicate, as do those of other investigators, that the intelligent, widespread use of this drug in pneumonia should result in a marked lowering of the gross mortality rate from this disease.

Sulfapyridine has usually been found to be less readily absorbed and more slowly excreted in human beings than is sulfanilamide. It is distributed in the tissues of the body in a manner somewhat similar to that noted for sulfanilamide. The percentage of sulfapyridine that is conjugated to the acetyl form in the tissues is frequently quite high. The fraction of the drug which is absorbed from the gastrointestinal tract is excreted mainly in the urine in which the drug exists as such, and as acetylsulfapyridine. Because of the variations in the absorption, the excretion and the acetylation of the drug, precise therapy by the peroral route is more difficult with sulfapyridine than it is with sulfanilamide.

The immediate effect of adequate doses of sulfapyridine in pneumonia is to cause a marked fall in the fever. The pulse and respirations return more slowly to normal than does the temperature. The physical signs of the disease may disappear rapidly or they may evolve in a manner similar to that noted in pneumonias of untreated patients. This makes it necessary to continue therapy until convalescence from the disease is well established, for otherwise a relapse of the infection may take place.

It has been possible to use peroral therapy alone in the majority of patients whom we have treated during the past year. However, in patients severely ill with pneumonia, or in those individuals who did not readily absorb the drug following peroral therapy, the intravenous use of the soluble monohydrate sodium salt of sulfapyridine has been a practical and very helpful therapeutic procedure. The toxic manifestations which we have observed in the course of sulfapyridine therapy have been essentially those previously noted in the course of therapy with sulfanilamide. Nausea and vomiting occur much more frequently when sulfapyridine is given. The drug does not cause acidosis. A new toxic manifestation, that of the formation of acetylsulfapyridine renal calculi with the production of pain and hematuria has been observed in the course of sulfapyridine therapy.

Conclusions

1. During the past year (1938–39) the case fatality rate in 139 adults ill with pneumococcal pneumonia in The Johns Hopkins Hospital was 7.2 per cent. We attribute this low death rate to the use of antipneumococcal serum, sulfapyridine, and serum and sulfapyridine in the treatment of pneumonia.

2. Sulfapyridine has proved to be a valuable chemotherapeutic agent in the treatment of pneumonia.

3. The drug is irregularly absorbed from the gastrointestinal tract in human beings.

4. A relatively large fraction of the sulfapyridine which is absorbed may be conjugated to acetylsulfapyridine.

5. The soluble sodium salt of sulfapyridine which may be given by the intravenous route is a valuable adjunct in the treatment of severe pneumococcal infections.

6. The therapeutic use of the drug in patients ill with pneumonia must be continued until convalescence is established, if relapses are to be avoided.

7. In certain individuals, the administration of sulfapyridine produces toxic manifestations similar to those previously described as occurring in the course of therapy with sulfanilamide.

8. Renal calculi, composed of acetylsulfapyridine, may form in the urinary tracts of patients who are receiving sulfapyridine.

9. The complete abandonment of the therapeutic use of type specific serum in pneumonia is not indicated in the light of our experience.

10. The widespread and intelligent use of the specific therapeutic agents now available for the treatment of pneumonia should cause a sharp drop in the gross mortality rate in this disease.

We are indebted to Lederle, Inc., and E. R. Squibb and Sons for certain of the antipneumococcal sera which were used in the treatment of these patients, to Eli Lilly and Company and the Calco Chemical Company, Inc. for the sodium sulfapyridine, and to the Calco Chemical Company, Inc. and Merck and Company for the sulfapyridine.

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THE CLINICAL MANIFESTATIONS OF THE VARIOUS TYPES OF RIGHT SIDED HEART FAILURE (COR PULMONALE) *

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Although the interdependence of the several cardiac chambers in the maintenance of efficient circulatory function is acknowledged, it is nevertheless recognized that the various anatomical and physiological disorders which disturb the cardiac function often affect, at least for a time, one side of the heart more than the other; and that in most instances the early clinical manifestations tend to indicate whether the right or the left ventricle is mainly involved. Furthermore, the recognition of the particular side of the heart initially affected often will furnish diagnostic evidence of the underlying pathological process as well as therapeutic indications for the adequate management of the case. The importance, therefore, of an understanding of the features distinguishing right and left ventricular failures, respectively, is apparent. Although a number of contributions have appeared in recent years on the subject of left ventricular failure,[1, 2, 3, 4] right ventricular failure has received relatively little attention. It is the purpose of this communication to present a résumé of the present day knowledge of the various features of strain and failure of the right side of the heart.

The term "cor pulmonale," originally intended to denote cardiac strain and failure directly due to pulmonary disease, may logically be employed in a broader sense to include all types of cardiac strain and failure in which the right side of the heart is importantly involved, either as the initial circulatory disorder (primary cor pulmonale) or as a consequence of an antecedent failure of the left side of the heart (secondary cor pulmonale).† In the majority of cases the immediate cause is an obstruction or increased

* Received for publication July 15, 1938.

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† The term "cor pulmonale" may be construed as signifying that the immediate cause of the cardiac disorder is a lesion disturbing the pulmonary circuit. Such a lesion may be located at any point between the mouths of the venae cavae on the right side of the heart and the mitral orifice on the left. Cor pulmonale in this sense would therefore include all instances of cardiac strain in which the right side is involved on the basis of pathological anatomy or physiology peculiar to that side. However, "cor pulmonale" cannot logically include right sided heart failure occurring simultaneously with failure of the left side of the heart brought about by conditions affecting the heart as a whole, as exemplified by the cardiopathies of hyperthyroidism, acute myocarditis, myxedema, anemia, beri-beri, prolonged paroxysmal tachycardia, and functional persistent auricular fibrillation. In some of these instances, particularly in the beri-beri heart, evidence of right sided heart failure (congestion of the systemic veins and liver) may predominate over pulmonary engorgement; and although the heart as a whole is much enlarged, the dilatation of the right auricle and ventricle as well as of the pulmonary artery may appear especially prominent in the roentgenogram.[5] This may be due to the lesser reserve of the musculature of the right chambers, or as suggested by Aalsmeer and Wenckebach,[6] to the fact that the left ventricle is functionally spared by the greatly reduced output of the right ventricle.

resistance to the blood flow within the lesser (pulmonary) circuit at any point between the pulmonary conus and the mitral valve. In a few instances, in the absence of direct obstruction, right sided strain and failure

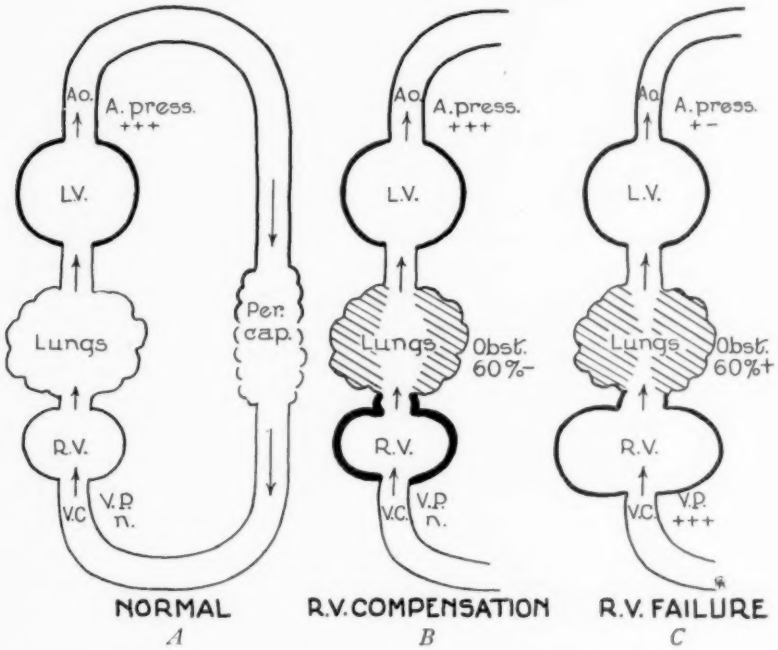

FIG. 1. Schematic drawing showing the mechanism of production of cor pulmonale in the stages of compensation and failure. *A*. Normal circulation. *B*. Strain of right ventricle due to obstruction of pulmonary vascular bed (less than 60 per cent). Hypertrophied right ventricle is shown in stage of compensation. The pulmonary resistance is successfully overcome and adequate ventricular output is maintained with normal systemic arterial and venous pressures. At this stage there may be no symptoms except roentgenographic evidence of dilatation of the pulmonary conus. *C*. Stage of decompensation (right ventricular failure). Pulmonary vascular narrowing exceeds 60 per cent, a degree of obstruction in excess of that for which the average right ventricle is able to compensate. The right ventricle is shown dilated with diminished ventricular output, low aortic pressure and increased systemic venous pressure.

may result from increased right ventricular output such as occurs in congenital septal defects and in organic tricuspid regurgitation.

THE GENERAL SYMPTOMS AND SIGNS OF COR PULMONALE

The symptoms and signs of cor pulmonale are of two categories: The first comprises the manifestations of the antecedent or associated cardiopulmonary disease; the second includes the disturbances produced directly by the hypertrophy, dilatation and failure of the right cardiac chambers.

I. The manifestations of the underlying cardiopulmonary disease are (1) cyanosis, (2) dyspnea, (3) polycythemia, (4) hemoptysis, (5) clubbing of the fingers and toes, and (6) the specific signs and symptoms of

the particular disease present, such as chronic bronchitis, emphysema, pulmonary fibrosis and other similar lesions.

II. The disturbances arising directly from the strain and failure of the right cardiac chambers are (1) increased venous pressure affecting the territories of both venae cavae and resulting in (a) engorgement of the superficial veins, (b) subcutaneous edema, (c) visceral congestion with palpable enlargement and tenderness of the liver, (d) transudation into the serous cavities, (e) oliguria with albumin and sometimes blood due to passive congestion of the kidneys, and (f) increased cerebrospinal pressure; (2) hypertrophy and dilatation of the right auricle, right ventricle and conus and dilatation of the pulmonary artery which are demonstrated most readily by roentgen-ray examination and often also by palpation (lower sternal

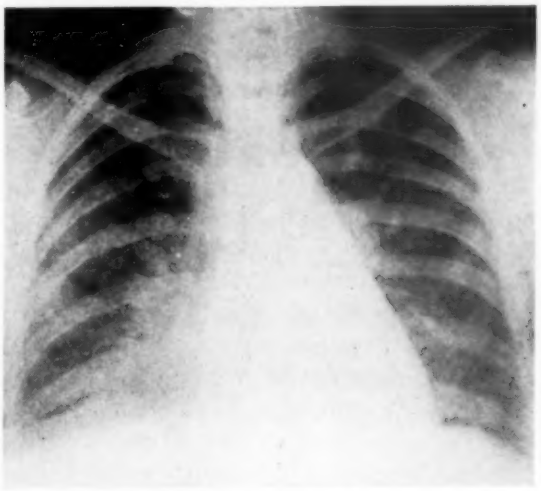

FIG. 2. Roentgenogram showing cardiac silhouette characteristic of cor pulmonale. Bulge in the region of the cardiac waist ("filling" of waist) is due to dilatation of pulmonary artery and conus.

thrust) and percussion (filling of waist); (3) accentuated pulmonic second sound and the presence in the left second and third interspaces of murmurs, thrills, and gallop rhythm; and (4) low systemic blood pressure.

The electrocardiogram often reveals right axis deviation. However, the hypertrophy of the right ventricle may be counterbalanced by an equal degree of left ventricular enlargement in which case no ventricular preponderance occurs. In some instances left axis deviation is encountered when the hypertrophy of the left ventricle exceeds that of the right.

PRIMARY COR PULMONALE

Although occurring less frequently than the secondary variety (the ratio being about one to five), primary cor pulmonale is symptomatically

the more important, since it is only in this type that the classical picture of isolated right sided heart strain is observed. From the standpoint of the clinical course as well as etiology there are recognized three subdivisions of primary cor pulmonale, the acute, the subacute, and the chronic.

Acute Cor Pulmonale.[7, 8] Acute cor pulmonale results from a sudden obstruction of the trunk or first branches of the pulmonary artery * by embolism or (rarely) by rapid thrombosis.[9] The onset is explosive with extreme suffocating dyspnea, cyanosis and often pain. The pain may be in the sternal region, on either side of the chest, or in the shoulders. In addition there are usually symptoms of severe shock, and (rarely) convulsions or coma may be present.

The objective findings are those of severe shock and, if the patient survives the initial attack, of strain and failure of the right side of the heart. There is a deep, almost black, cyanosis or an ashy paleness and profuse perspiration. The pulse is rapid and very weak. The blood pressure is low. Dilatation of the pulmonary artery and conus may be demonstrable by percussion, palpation, or by the roentgenogram. The second pulmonic sound is frequently accentuated and a gallop rhythm may be present. Occasionally a pericardial friction rub may be heard with maximal intensity in the region of the left second, third and fourth interspaces. The lungs may show nothing abnormal, but often râles are present. Less frequently fluid may be found at the bases, and occasionally widespread pulmonary edema may develop. Fever and leukocytosis are often present.

The clinical picture of acute cor pulmonale strongly resembles that of acute coronary occlusion. During the first 12 to 24 hours the differential diagnosis is often extremely difficult. Pain is more apt to dominate the picture of coronary occlusion, dyspnea that of pulmonary embolism. McGinn and White [7] noted the following electrocardiographic changes which they regard as characteristic of acute cor pulmonale: "The presence of a Q-wave and late inversion of the T-wave in Lead III, the rather low origin of the T-wave with a gradual staircase ascent of the ST interval in Lead II, a prominent S-wave and a slightly low origin of the T-wave in Lead I, and an upright T-wave (with inverted P and QRS waves) in Lead IV." In some of their cases there was definite right axis deviation. In none was left axis deviation present at the time of the acute episode. These electrocardiographic changes are temporary and usually disappear within 48 hours after the attack.

The prognosis is grave, the mortality being in excess of 50 per cent; most of the fatal cases die within 30 minutes to 24 hours after the occlusion. However, the patients who survive usually make a complete recovery.

Treatment [10, 11] consists of the immediate administration of antispasmodic substances, such as papaverine (one-half grain intravenously) or atropine, and enough morphine to control pain. Oxygen is indicated in the

* In rare instances emboli involving the minute branches or the capillaries may be so numerous as to produce acute right ventricular failure similar to that resulting from an obstruction of the primary branches.[5]

presence of cyanosis and dyspnea. Embolectomy [12] by the Trendelenburg operation [13, 14] has been attempted and in rare instances has proved successful. However, as yet, this procedure must be viewed as strictly experimental.

Since the most common cause of pulmonary embolism is venous thrombosis in the lower extremities,* prevention of the latter becomes a matter of prime importance. Factors favoring venous thrombosis are circulatory stasis, dehydration and trauma. Such conditions are most apt to develop in persons of relatively advanced years as a result of surgical operations (especially abdominal or pelvic) or accidents. Circulatory insufficiency is an important contributing factor. The following preventive measures are recommended by Barnes [10] for postoperative cases, especially for patients more than 40 years of age: "The patient is placed in the Trendelenburg position for the first 24 hours after operation. Carbon dioxide is administered by inhalation several times in the day and night for the first 48 hours. Frequent deep breathing exercises are urged in every case. Attempts at early coughing are encouraged as much as possible. Extreme care is observed to keep the patient's legs warm at the operation, during his transfer to his room, and after his return to bed. Frequent massage of the legs is practiced during the first 48 hours and twice daily thereafter until the patient is out of bed. Passive and active movements of the extremities are insisted on at stated intervals from the time the patient is returned to his room until he is out of bed." Prolonged recumbency should be avoided and adequate measures employed to combat circulatory failure. Desiccated thyroid may be administered cautiously in suitable cases to increase the velocity of the venous return.

Many of these measures are also applicable to medical cases in which prolonged inactivity is necessary.

Subacute Cor Pulmonale. Subacute cor pulmonale is characterized by the rapid development of signs and symptoms of right ventricular strain in a patient who gives no history of antecedent cardio-pulmonary disease or of any other condition known to be capable of producing strain of the right side of the heart. Cases belonging to this group have been reported by Schmidt,[15] Krutzsch,[16] Greenspan,[17] and Brill and Robertson.[18] The latter authors recently have summarized the clinical and pathological features of this rare condition and suggested the term "subacute cor pulmonale" as most descriptive of its clinical manifestations. The cause is a rapidly progressive narrowing and obliteration of the pulmonary vascular bed by a metastatic carcinomatous invasion of the pulmonary lymphatics and arterioles. The process of vascular narrowing is further accelerated by secondary intimal connective tissue proliferation and thrombosis (carcinomatous lymphangitis and endarteritis).

* The veins of the gastrocnemius and soleus muscles are frequently found to be the seat of such thrombosis and the source of pulmonary embolism. This observation originally made by Erdheim (Vienna) has been amply confirmed in our clinic.

The dominant symptoms are dyspnea and unproductive cough, which, though mild at the onset, tend to progress rapidly, and after continuing with increasing severity for two weeks to two months (rarely longer) end fatally. Death occurs more or less suddenly with symptoms of circulatory collapse and signs of acute right heart failure.

This syndrome is distinguished from the acute cor pulmonale by the more gradual onset without pain or shock and by the relatively more prolonged and progressive course. It is differentiated from the chronic types of cor pulmonale by the absence of antecedent cardio-pulmonary disease and by the much shorter course than is usual in the chronic types. In the latter the duration of the cardio-pulmonary symptoms varies from six months to more than five years with an average duration of two years.

So far as is now known, metastatic carcinoma is the only pathological process which is capable of producing the clinical picture of subacute cor pulmonale. In most of the reported cases the primary lesion was a scirrhous carcinoma of the stomach. The patients were all relatively young subjects 36 to 40 years of age. Some gave a history of "peptic ulcer," others complained of but vague gastric discomfort for a period of several months to one year or longer. In most instances the primary lesion and the nature of the cardiac strain remained unsuspected during life.

It is possible that cases represented by this clinical syndrome occur more frequently than might be inferred from the foregoing account. In recent reviews Wu [19] and Jarcho [20] each collected from the literature a large number of cases of carcinomatous lymphangitis involving the pulmonary vascular bed in a manner capable of producing the picture of subacute cor pulmonale. Although in most of these the involvement of the heart clinically was not mentioned, the symptoms recounted in a number of the quoted reports suggest the possibility that in some of those cases the full picture of subacute cor pulmonale might have been present.

Chronic Primary Cor Pulmonale. Chronic primary cor pulmonale is of manifold etiology. The most important causes are mitral stenosis, extensive pulmonary fibrosis (on the basis of pneumonoconiosis, tuberculosis or other chronic infections), and severe emphysema secondary to asthma, chronic bronchitis or some other pulmonary disease. Less frequent causes are marked deformity of the chest (kyphoscoliosis) and certain congenital cardiac lesions; namely, defects of the pulmonary valve, patent ductus arteriosus and septal defects. Still rarer causes are organic tricuspid regurgitation and primary pulmonary arteriosclerosis.

The clinical manifestations are those enumerated in the earlier part of the paper as " the general symptoms and signs of cor pulmonale." In the early stages, before actual cardiac failure supervenes, only the symptoms and signs related to the associated cardio-pulmonary pathology may be present, and the involvement of the right ventricle may be difficult to demonstrate except by roentgenographic disclosure of the dilatation of the pulmonary artery and conus. With the onset of right ventricular failure the classical picture

of chronic cor pulmonale becomes complete. The grouping of the symptoms and their severity will depend upon the type and extent of the underlying cardio-pulmonary disease. In cases of long-standing with diffuse lung involvement including pulmonary vascular sclerosis and hypertension, there sometimes develops an extreme, almost black cyanosis ("cardiacos negros" of Ayerza and Arrillaga [21]), along with the entire picture of chronic cor pulmonale described above, including also cerebral manifestations (headache, mental confusion and somnolence) and attacks of severe anginal pain, radiating deeply toward the back (hypercyanotic angina). This syndrome, sometimes referred to as Ayerza's disease, represents merely an extreme degree of chronic cor pulmonale which may arise from any of the etiologic factors enumerated above when severe enough to produce extensive pulmonary arteriosclerosis with hypertension and marked narrowing of the pulmonary vascular bed.

The course of chronic primary cor pulmonale is progressive but slow, extending over a period of years. Most of the patients die of an intercurrent infection, especially pneumonia; some die of congestive heart failure; a few die either suddenly or in acute circulatory collapse similar to that which often is observed in the acute and subacute types of cor pulmonale. In this latter mode of death the patient while apparently comfortable, suddenly becomes breathless and panicky. The pulse becomes rapid and weak. Death occurs usually within one to several hours. As was pointed out in a previous communication [18] the sudden circulatory collapse probably represents a stage in the obstructive pulmonary process in which the narrowing of the pulmonary vascular bed reaches a degree beyond that compatible with life (more than 60 per cent narrowing). At such a high degree of pulmonary vascular obstruction, due to the marked reduction in the right ventricular output and consequent lowering of the aortic pressure, a diminished coronary flow occurs which causes further weakening of the right ventricle. A vicious circle is thus established resulting either in instant death (perhaps due to failure of the cardiac pacemakers [22]) or in acute circulatory collapse with death in a few hours.

The treatment of chronic cor pulmonale consists of the management of the underlying pulmonary disease and of the myocardial insufficiency when present. The treatment of the latter includes the usual measures for congestive failure, namely, rest, dietary restriction, digitalis and diuretics. Oxygen is indicated in the presence of dyspnea or cyanosis whether of cardiac or of pulmonary origin. Additional therapy for the underlying pulmonary disease will be determined, of course, by the specific disturbance present. In many instances the pathological process is irreversible and little can be expected from this part of the treatment. However, in all cases digitalis and diuretics should be tried; much relief is often obtained by the removal of occult edema, even if no visible congestion is present.

Secondary Cor Pulmonale

Although the most common type of right sided heart failure,[23] secondary cor pulmonale, for the purpose of this discussion, requires little special consideration, since it merely represents an advanced stage of general heart failure. The immediate cause of secondary cor pulmonale is the pulmonary congestion and consequent increased resistance to the pulmonary circulation resulting from an antecedent failure of the left ventricle.

The remote causes of secondary cor pulmonale are the conditions which are commonly responsible for failure of the left side of the heart. The most important of these are (1) hypertensive disease, (2) deformities of the aortic valve, and (3) coronary artery disease. The latter, although affecting the heart as a whole, usually involves the left ventricle to a greater extent than the right, and symptoms of pulmonary congestion (dyspnea, continuous or paroxysmal, diminished vital capacity, etc.) which are pro-

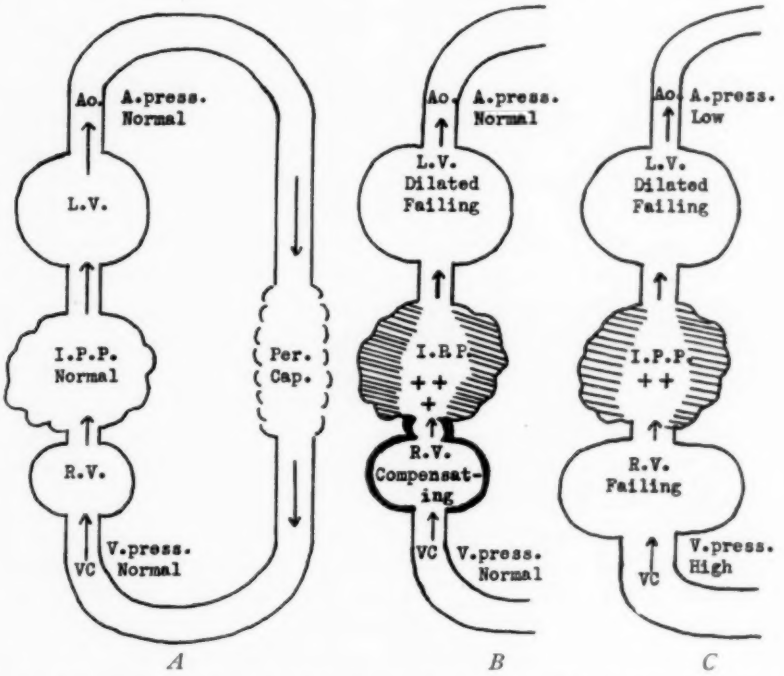

Fig. 3. Schematic drawing showing the mechanism of production of right ventricular failure secondary to failure of the left ventricle (secondary cor pulmonale). *A*. Normal circulation. *B*. Strain of the right ventricle in the stage of compensation. The strain is due to the increased intrapulmonary pressure resulting from failure of the left ventricle. The aortic pressure, however, remains normal or only moderately lowered and the systemic venous pressure likewise remains normal as long as the hypertrophied right ventricle is compensating and its output continues at normal or above normal levels. The increased intrapulmonary pressure is responsible for the accentuated second pulmonic sound noted clinically. *C*. Finally the right ventricle dilates and fails; the systemic venous pressure becomes greatly increased (resulting in peripheral edema noted clinically), and the aortic pressure is significantly lowered. There is also a moderate lowering in the intrapulmonary pressure which sometimes results in a slight improvement in the dyspnea.

duced by failure of the left ventricle often precede the appearance of symptoms due to failure of the right ventricle (peripheral edema, congestion of the liver and distention of the superficial veins). In most of these instances but a short time (hours, days, or weeks) elapses between the onset of left ventricular failure and the first manifestations of failure of the right side of the heart. On the other hand in hypertensive disease and in some cases of aortic disease, symptoms of left ventricular failure may prevail over a more extended period before signs of right sided heart failure become manifest. Not infrequently breathlessness or attacks of paroxysmal dyspnea continue for years and death occurs either during such a paroxysm or as a result of a complicating coronary thrombosis without peripheral edema ever making its appearance. In some instances, the onset of failure of the right ventricle results in an improvement of the pulmonary congestion with consequent relief of breathlessness and disappearance or lessening in the frequency of attacks of paroxysmal dyspnea.

The treatment consists of the standard measures employed in congestive failure, including rest, digitalis, dietary restriction, diuretics, venesection and oxygen. The prognosis depends largely upon the underlying condition responsible for the left ventricular failure. In syphilitic aortic disease, after congestive failure is well established, but little temporary benefit can be secured from any mode of therapy, and death may be expected within one to two years. On the other hand in cases of essential hypertension without significant renal involvement extremely gratifying results can be obtained from the judicious application of the aforenamed therapeutic procedures, and relatively good health may be maintained over a period of years.

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SOME PROFESSIONAL AND SOCIAL TRENDS IN AMERICAN MEDICINE*

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It is a matter of difficulty, if the task be not wholly impossible, for the individual worker in any field of medical practice correctly to evaluate the multitudinous changes which are constantly occurring in this field of human endeavor. It is but a comparatively short time since didactic instruction compassed the training for a career in medicine and the armamentarium of the doctor consisted of a thermometer, a stethoscope, an obstetrical bag and a few instruments. The increase in medical knowledge during the present century has been so vast and the changes in social, economic and scientific aspects of modern civilization have progressed so rapidly as to demand a complete reorientation for an appreciation of their significance and implications. While the physician remains an individualist so far as the application of curative medicine is concerned, he cannot remain oblivious to other important elements in our social fabric since the problems of illness which he solves for the individual have an interest for the community as a whole, particularly in their preventive and social aspects. This changed conception of professional obligation has brought to the fore many problems, the solution of which is not yet in sight, but which demand our earnest consideration and study. In order that I may confine my remarks to something approaching a logical order of sequence, my subject will be discussed under two headings, scientific and social trends.

Scientific Trends

Having been reared professionally in the waning shadow of one school of thought, that founded on clinical observation alone, and in this golden age seeing the beautiful fruition of that built on accurate scientific knowledge, I can but pay in an inadequate manner a feeble tribute to the votaries of science in bringing about this transformation and increasing the sum total of human knowledge. This accretion has followed three pathways, first the anatomical, second the pathological, and today the physiological and biochemical. "The most significant trend of surgery has been the attempt to control, ameliorate, abort and prevent those condition which are known or suspected to be dependent on disturbed physiological processes." This is notably true in the surgery of the sympathetic nervous system with the control of vasomotor spasm, the surgery of peptic ulcer, in the surgical treatment of conditions dependent on abnormal activity of the ductless glands and in the collapse therapy of pulmonary tuberculosis. Many factors for the safety of surgical patients have been developed in the preoperative

* Read at the New Orleans meeting of the American College of Physicians, March 27, 1939.

care, the technical procedure and the postoperative care with a consequent reduction in mortality of appreciable degree. The exact tests evolved in the clinical and experimental laboratories, of which there are many, when intelligently correlated with the history and physical findings, permit of greater accuracy in diagnosis and prognosis and of greater exactitude in therapy than ever known before. The many agents for inducing anesthesia, with or without the employment of synergistic drugs, allow a selection of the one best suited to the patient and the disease, while contributing materially both to comfort and safety. The brilliance of the accomplishments in the highly specialized fields of surgery is but enhanced by the former belief that they were unattainable. Thoracic surgery now offers repair of cardiac wounds, pericardiectomy in Pick's disease, an experimental effort to supplement coronary circulation, pneumonectomy in whole or in part for the relief of bronchiectasis and tumor, and collapse therapy for pulmonary tuberculosis by means of intrapleural pneumolysis, extrapleural apicolysis, interruption of the phrenic nerve and thoracoplasty partial or complete. Neurosurgery successfully ventures the exploration of the innermost recesses of the brain for the relief of pressure and the removal of tumors, even daring the ablation of a lobe or of an entire hemisphere. Sympathectomy finds an ever widening field of usefulness in correcting disorders dependent upon perverted nerve function and impeded vascular channels. The era of speed and the removal of large portions of the body to get rid of a small diseased part has been superseded by a careful meticulous technic which sacrifices no healthy tissue and considers every cell valuable unless diseased. The trend toward the preservation of healthy tissue is well illustrated by the employment of irradiation in the therapy of certain neoplasms, both benign and malignant. Well established major surgical procedures have been abandoned in the search for simpler methods which will reduce mortality and morbidity as instanced in the transurethral resection of the prostate and the injection of sclerosing substances in various conditions. Chemical research is responsible for much of the changing order in medicine. It has altered our conceptions of the physical structure of living tissue, has shown the chemical changes which take place in the discharge of body and organ functions, and increased our knowledge of the chemical substances which may control such activities. The relation of the diseases of metabolism and nutrition to vitamin deficiency and hormonal dysfunction, the rôle of the pancreas in carbohydrate metabolism, of the liver and stomach in hematopoiesis, of the hypophysis in influencing growth and obesity, and of the thyroid in influencing metabolism are beautiful illustrations of the knowledge garnered by this type of research. Increasing knowledge of the endocrine hormones is opening up a field for study and therapy which, if one may venture a prophecy, is but in its infancy. Pneumonia for the first time in its history is being made to give ground by accurate typing and appropriate sera. Modern medical thought with relation to the infectious diseases is first directed toward prophylaxis. Failing

this ideal, a specific remedy, either chemical or biologic, is sought. The present wave of sulfanilamide therapy evinces the eagerness with which the profession awaits any chemical or serum purported to possess specific properties. The fact that heart disease after the age of 40 is the leading cause of death has focused attention on its prevention, early detection and proper treatment. It is interesting to note that total thyroidectomy is being practiced in congestive heart failure with the idea of lessening metabolism and thus decreasing the cardiac load, another instance of the physiological approach to the solution of medical problems. Psychiatry throughout the past century has been a veritable "terra incognita": only when the injunction, "sit lux" of modern science was applied to it has it emerged from the gloom and darkness with which it was enshrouded. Hospitals staffed by competent medical personnel, registered nurses, and aides versed and trained in psychiatry are meeting the challenge of the disordered mind with an orderly mind skilled in the application of scientific, psychiatric knowledge.

One of the most significant trends is to be found in preventive medicine. While the major responsibility in this field devolves upon the United States Public Health Service and the State and County Health Officers, the physician in practice has come to a realization that his obligation to society demands an extension of activity far beyond the intimate personal relationship between the individual patient and himself to the broader field of preventive medicine, widening his sphere of responsibility from the care of patients to that of the community of which the patients are a part. An interested lay public participates in this program through many worthwhile organizations. Legal enactments permitting sterilization of the unfit and requiring a clean bill of health on the part of those who would enter the marriage state, while more specifically in the field of eugenics, give further evidence of lay interest. It has been truly said that preventive medicine forms the keystone of the triumphal arch of modern civilization since the prevention of disease, and therefore the prevention of suffering and death, is a more important and glorious achievement than the cure of the individual or the reduction of disease mortality. A noteworthy accomplishment, largely attributable to prevention, has been the increase in life expectancy which now stands at 62 years. But this indicates that we are slowly developing a society in which old age with its degenerative lesions will represent a constantly increasing percentage of disease.

Social Trends

In the changing social thought of the last few years much has come about that is at wide variance with what heretofore had been regarded as fixed and established. Industrial disability compensation, unemployment compensation and old age pensions are illustrative answers to the biblical question, "Am I my brother's keeper?" With the present urge to procure a greater distribution of social justice, there is in some quarters a tendency to go to the extreme of complete socialization, in which effort medicine

has been selected as a proving ground. If human intelligence and scientific medical knowledge could be dispensed in boxes and crates as a market commodity, its distribution could be fitted into such a concept of economics. The fundamental concept in both ethics and economics is that of value. In economics the ultimate test of value is the amount of goods which will be consumed or the medium of exchange which will be paid in the market. Ethics embraces a wider conception and makes its ultimate test of value the effect on the individual and the society in which he lives. If medical relations are to be ethical—that is, in furtherance of the ultimate good of the patient and of the public welfare—they must be between the patient who is to be treated and the physician trained according to established standards and having access to the accumulated knowledge of the ages. The advances in the distribution of medical knowledge during the past 50 years have been evolutionary, developing means to meet needs as they have arisen. The record is one of which to be proud; mortality has been reduced 50 per cent and life expectancy has been increased 100 per cent. During 1938 an all time low has been attained in the mortality of every disease other than heart disease and cancer. The explanation for their increased mortality becomes readily apparent when we bear in mind the number of people now living in the age groups above 40 years, the period in which these diseases exact their greatest toll. Even with this remarkable accomplishment of American medicine, no agency knows better than the medical profession of the lag or gap that exists between accumulated medical knowledge and its equable distribution. And no agency is more interested in bridging this gap, granting that it be done in a way to maintain the ethical institutions of Medicine. As far back as 1875 the House of Delegates of the American Medical Association recommended the formation of a Department of Health with a cabinet officer at its head, to the end that all health activities might be coördinated and correlated. During the passing years it has repeatedly urged consideration of this proposal. During the same years there has been an increase in participation of governmental agencies in health activities scattered through many departments, the Public Health Service in the Department of the Treasury, Maternal and Child Welfare in the Department of Labor, Food and Drugs in the Department of Agriculture, the care of the Indians and the insane in the Department of the Interior, the care of the Army and Navy in their own Departments, the care of the veterans in the Veterans' Bureau, the care of the indigent farmers in the Resettlement Administration, and so on through more than 20 different agencies involving the expenditure of many millions of dollars. The President of the United States appointed an Interdepartmental Committee to Coördinate the Health and Welfare Activities of the Government, which in turn appointed Technical Committees to assist in the study of its problems, one of which devoted its activities to the study of Medical Care. The National Health Survey, upon which some of its conclusions were based, was a spot survey made largely by WPA workers covering four

million rural and urban inhabitants in 17 states. By using the findings of this survey as an index to the needs of the country as a whole, the Technical Committee assembled data and reached conclusions that in many instances are at variance with the data and information collected by the American Medical Association. If it be true that one-third of the population is poorly clothed, poorly housed, poorly fed and without medical care, the problem presented thereby is even more social and economic than medical. The maternal death rate among the whites compares favorably with that of any other country, while that among the negroes is inordinately high. Many of the negroes live in squalor, are poorly clothed, poorly housed, undernourished and rachitic, and without medical care even though it is often available: that such conditions exist is an indictment of society but certainly not of the medical profession. The availability of hospital service is another feature upon which there is a rather marked discrepancy. But regardless of its errors the report contains factual data upon which all agree and which form a basis for the consideration and study of all agencies in formulating a program for the wider distribution of medical care. In July 1938 a National Health Conference was held in Washington under the auspices of the Interdepartmental Committee at which recommendations for a National Health Program were proposed, envisaging a comprehensive participation by the federal government in health activities. Briefly, the program provided for an expansion of public health service and of maternal and child welfare; expansion and construction of hospital facilities and diagnostic centers; medical care for the medical needy; aid to the states in developing plans for medical care on a tax-paid or compulsory insurance basis; and payments to the worker for disability resulting from sickness. The development of the proposed program was to be a gradual one with completion in 10 years, at which time it would involve an expenditure of $850,000,000 annually. At a special meeting of the House of Delegates of the American Medical Association held in September 1938, approval was given to expansion of public health service and maternal and child welfare where need could be shown; approval to hospital and diagnostic center construction where need could be shown, recommending, however, utilization of existing facilities to the utmost; approval of medical care to the indigent and medically indigent where need could be shown; approval of the principle of assistance to the worker for temporary disability resulting from illness; approval of group hospitalization and voluntary insurance. But there was unqualified disapproval of tax-paid or compulsory sickness insurance. The special committee appointed by the House of Delegates held two conferences with the Interdepartmental Committee, one on October 31 and one on January 15. Since the Interdepartmental Committee did not at either sitting submit a draft of the proposed legislative enactment for the translation of its recommendations into activity, the discussions were of necessity limited to principles. There was agreement in principle on the objectives of four of the recommendations but disagreement on Recom-

mendation IV which provides federal help for the states initiating studies and plans for the care of all their people on a tax paid basis. Compulsory sickness insurance is a more appealing and euphonious title than the one which accurately identifies it, namely, sickness tax. Mr. Falk of the Technical Committee set the income level at which compulsory plans would operate at $3000.00 or less. Federal statistics reveal that but 7 per cent of the population enjoy an income above this amount! If and when a compulsory plan becomes operative in all the states at this level, 93 per cent, or 120,000,000 of the population will be covered thereby. On January 23 the President presented to the Congress his message on the National Health Program with a recommendation for its careful consideration and study. On February 28 Senator Wagner of New York introduced into the Senate of the United States a bill, S. 1620, entitled "A bill to provide for the general welfare by enabling the several states to make more adequate provision for public health, prevention and control of disease, maternal and child health services, construction and maintenance of needed hospitals and health centers, care of the sick, disability insurance and training of personnel." Although the bill is actually an amendment to the Social Security Act, the bill proposes that if it is enacted it be called the "National Health Act of 1939." Assuming that this bill has the endorsement of the federal agencies responsible for the National Health Program, it has afforded opportunity to study the means by which it proposes to put into effect the recommendations of the Interdepartmental Committee and by comparison to see how far it harmonizes with the approval in principle given by the House of Delegates at its special session. The American Medical Association at no time expressed its opinion upon the amounts of money to be expended in such a program but it is of interest to note that the Wagner Bill proposes an expenditure of $98,250,000 for the fiscal year of 1940, $123,500,000 for the fiscal year of 1941, and $334,000,000 for the fiscal year of 1942 with no limit in the amounts during 1941 and 1942 for public health work, for grants for mental and tuberculous hospitals, for grants for medical care, for grants for temporary disability compensation, and for administration: and further that for the fiscal years subsequent to 1942 there is no specified limit for expenditure for the accomplishment of any of the purposes of the Act. While no specific mention is made of compulsory sickness insurance, the measure introduces the principle of allotment of federal money to the individual states for medical care, by the Social Security Board, without specifying the means to be used in the individual states for providing such service other than to demand the approval of the Social Security Board, being silent as to the permissible extensions and improvements of medical care that a state may make and as to whether such care shall be provided through a state medical service, or by a system of state health insurance, or by payment for services on a fee basis. The American Medical Association has at no time suggested an administrative agency for the National Health Program but has stressed

its opinion that such be developed within state agencies and state medical bodies. The Wagner Bill specifies three administrative agencies, the Children's Bureau, the United States Public Health Service, and the Social Security Board with final full authority resting in each. The advisory councils mentioned in the bill are vague as to their membership, their duties and their responsibilities. Granting the occurrence in a rural or isolated community of diseases, which from their classification would come under each and all three of these proposed agencies, satisfactory and competent administration would seem extremely difficult if not impossible. Such a contingency is another argument in support of the contention of the American Medical Association that a Secretary of Health, a unified agency for the correlation of all health activities is a necessity. The bill does not provide for means of determining the local need for the various services it proposes to furnish, a matter of importance repeatedly emphasized by the House of Delegates. No stipulation is made as to the utilization and improvement of existing hospitals in the face of the fact that the hospitals of this country constantly show a 30 per cent bed vacancy. These are some of the points that demand our consideration and study in aiding in the development of a health program for the nation, an intent to which we are by knowledge, experience and conviction committed, its fundamental objectives being an expansion of public health, maternal and child welfare services, approved care to the aged and medically indigent, and an extension of hospital and diagnostic facilities.

CASE REPORTS

SO-CALLED CHOLANGEITIS LENTA: REPORT OF A CASE DYING WITH ULCERATIVE ENDOCARDITIS*

By O. H. Perry Pepper, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

Chronic cholangeitis is one of those subjects about which everyone knows the same facts—but no one knows very many. Opinions differ in the current textbooks: Osler states that chronic cholangeitis may possibly occur as a sequel to an acute process but that it is usually secondary to common duct obstruction; Meakins relates it to a previous acute cholangeitis; Rehfuss, to acute cholecystitis or common duct obstruction. Bloomfield does not discuss the chronic forms. Stengel and Kern in the Nelson System describe only catarrhal jaundice and suppurative cholangeitis.

Rolleston and McNee,[1] Samuel Weiss [2] and other writers of authoritative monographs divide the condition which they term "chronic catarrhal cholangeitis" into those cases with calculus and those without—the latter group again being subdivided into cholangeitis of the extrahepatic ducts and of the intrahepatic ducts. This latter group is stated to arise from poisons or bacteria brought to the liver by the portal vein or the hepatic artery. As predisposing conditions portal cirrhosis, chronic venous engorgement, hepatitis and hepatic malignancy are mentioned.

From this sampling of the views of authoritative writers on this subject, it is easy to see the lack of definite knowledge. Some consider chronic cholangeitis identical or a part of catarrhal jaundice, others derive it from acute suppurative cholangeitis. In view of this confusion, it is not surprising that efforts have been made to describe certain sub-groups of cholangeitis. Perhaps the most interesting of these types is so-called cholangeitis lenta. This is interesting not only because of the concept involved, but also because of the extensive literature on cholangeitis lenta in German and Italian. The only English references to this term which I have found occur in an article on gall-bladder disease by Held [3] who reports a case due to *Streptococcus viridans* and in the Year Book for Medicine for 1934 in which Eusterman [4] abstracted a German article by Harnisch.[5]

The term "cholangeitis lenta" was chosen in 1921 by Schottmüller [6] as might be expected to describe a special type of infectious cholangeitis which was thought by him to present many analogies to endocarditis lenta. According to those who have written on this subject, this form of infection of the finer biliary passages develops as a primary condition, probably from ascending infection; it is not a suppurative process; it develops in the absence of gall stones and resembles endocarditis lenta. This resemblance rests on the insidious onset, the picture of slow sepsis with fever, anemia and splenomegaly and the prolonged course. Furthermore, the infecting bacterium is a streptococcus—often but not always the *Streptococcus viridans*—although some of the writers insist

* Received for publication May 27, 1938.

that the term cholangeitis lenta can be used only if the streptococcus is of the viridans variety. Others feel that it is the course and clinical picture which justify the term rather than the exact type of bacterium.

There is nothing new in the fact that among the infecting agents causing cholangeitis various types of streptococci are occasionally found. However, our literature has not stressed streptococcal cholangeitis as an entity nor the form to which others have applied the term "lenta." Even if we do not approve of the term "cholangeitis lenta," there may be something of value in the concept of a type of streptococcal cholangeitis with many analogies to endocarditis lenta, although the prognosis may be better.

The individual articles in the literature on cholangeitis lenta scarcely need to be reviewed at this time but one or two deserve mention. Eickhoff,[7] in 1922, was an influential advocate of the new entity but based his arguments chiefly on the similarities of this type of cholangeitis with endocarditis lenta, claiming that both were caused by the same *Streptococcus viridans*. Loewenhardt,[8] however, in the next year applied the term to cases due to other bacterial forms, and Hedinger,[9] in 1924, used the term for a case in which the infecting organism was the colon bacillus and stressed the possibility of a transition of the process into biliary cirrhosis. Umber [10] reported a case in which the infection was with paratyphoid B. It was at about this time that Aschoff emphasized the frequency of biliary infections by intestinal bacteria and d'Antona [11] emphasized this source of the infection in cholangeitis lenta. Rössle [12] in the section on inflammation of the liver in Henke and Lubarsch devotes half the space allotted to chronic cholangeitis to the "lenta" form.

Not all of the writers on this subject are unanimous in accepting the syndrome; for example, Sotgiu,[13] in 1933, felt that only a few of the reported cases deserved to be so diagnosed. However, the same year Harnisch [5] attempted to describe a characteristic picture for the disease. Still more recently, La Manna [14] has reviewed the evidence and comes to the conclusion that the diagnosis cholangeitis lenta is justified only if the patient presents the picture of slow sepsis and if proof is obtained of the presence of chronic cholangeitis. Rosenthal,[15] in his monograph in 1934, mentions the use of the term in cases which resemble a chronic sepsis and agrees that other bacterial forms than the *Streptococcus viridans* may be responsible. In Eppinger's [16] excellent book he states that although he has never seen such a case the diagnosis of cholangeitis lenta should not be difficult because of the obvious septic syndrome with fever, endocarditis and nephritis. He does not amplify this final statement which is unfortunate in view of the case which aroused our interest in this subject.

Case Report

The patient, a 36 year old janitor of good habits, entered the Medical Division of the University Hospital because of jaundice and weakness. At the age of seven he had suffered an attack of rheumatic fever with residual mitral damage. In recent years, he had some dyspnea on exertion and occasionally ankle edema and hemoptysis. A year before admission an episode of distinct cardiac decompensation occurred but was entirely relieved by digitalis which he continued until the appearance of the present illness, two months prior to admission. Jaundice, weakness and loss of weight increased rapidly and he came to us with a tentative diagnosis of carcinoma of the head of the pancreas.

In the Hospital the outstanding findings were intense jaundice, marked emaciation and mitral heart disease with auricular fibrillation but without failure of compensation. The abdomen seemed distended, there was some little tenderness and rigidity in the right upper quadrant, but no enlargement of the liver or spleen could be demonstrated. There was only a trifling anemia and no leukocytosis. Blood culture, serologic tests for syphilis and a variety of other laboratory investigations and

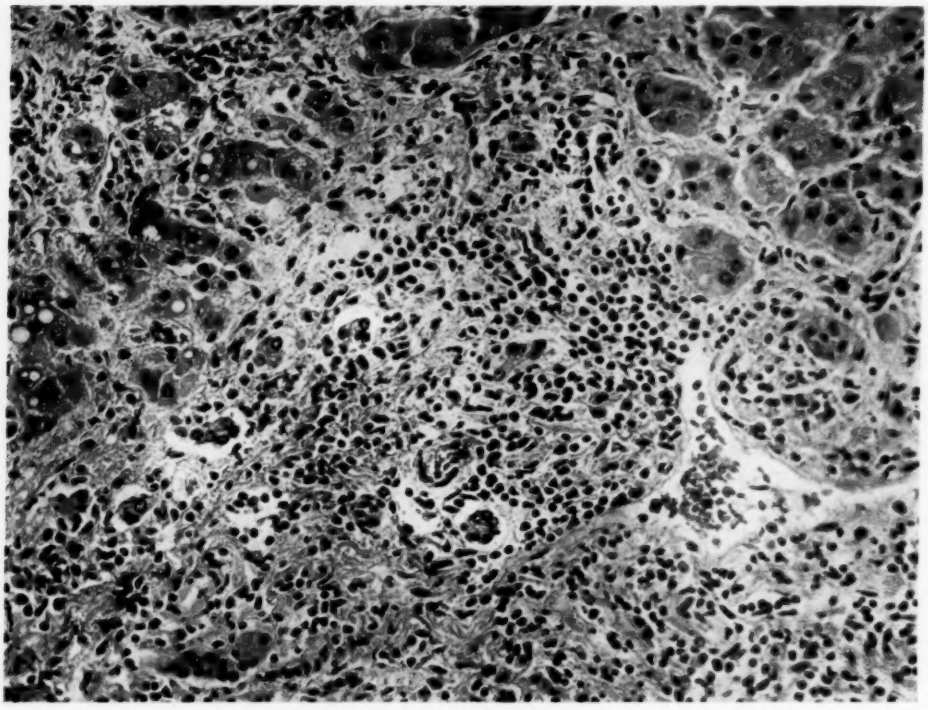

FIG. 1. Section of liver stained with hematoxylin-eosin (high power).

roentgen-rays which need not be detailed were negative. The van den Bergh test gave an immediate direct reaction with 14 units indirect. There was some bile in the stools; the biliary drainage showed nothing significant except for the presence of many pus cells. The patient did not appear seriously ill; there was a moderate irregular fever.

It was agreed that the circulatory state could not explain the jaundice; some felt that the diagnosis was long-standing catarrhal jaundice, others favored stone, still others malignancy. For a month conditions changed but little and surgical exploration was thought advisable. At operation, the gall bladder and common duct were found normal, no calculi were found; the liver, however, was distinctly abnormal, the surface being grayish and irregular. The operative diagnosis was cirrhosis of the liver.

Three weeks after operation, the patient was transferred back to the medical ward. There had been little or no fever for a week before transfer. However, soon after transfer January 11, 1937, fever returned and the second phase of this patient's illness developed. The fever was apparently not related to the surgical wound; the leukocyte count was not elevated. There was no distinct change in the cardiac or circulatory conditions, and various laboratory studies failed to shed any light on the

cause of the irregular fever which continued in the neighborhood of 102° F. After two weeks a few red cells began to appear in the urine, and after another two weeks the blood culture was positive for the first time and gave a growth of beta hemolytic streptococci. Still later, macrophages appeared in the blood. Death occurred two months after the development of this phase of the illness.

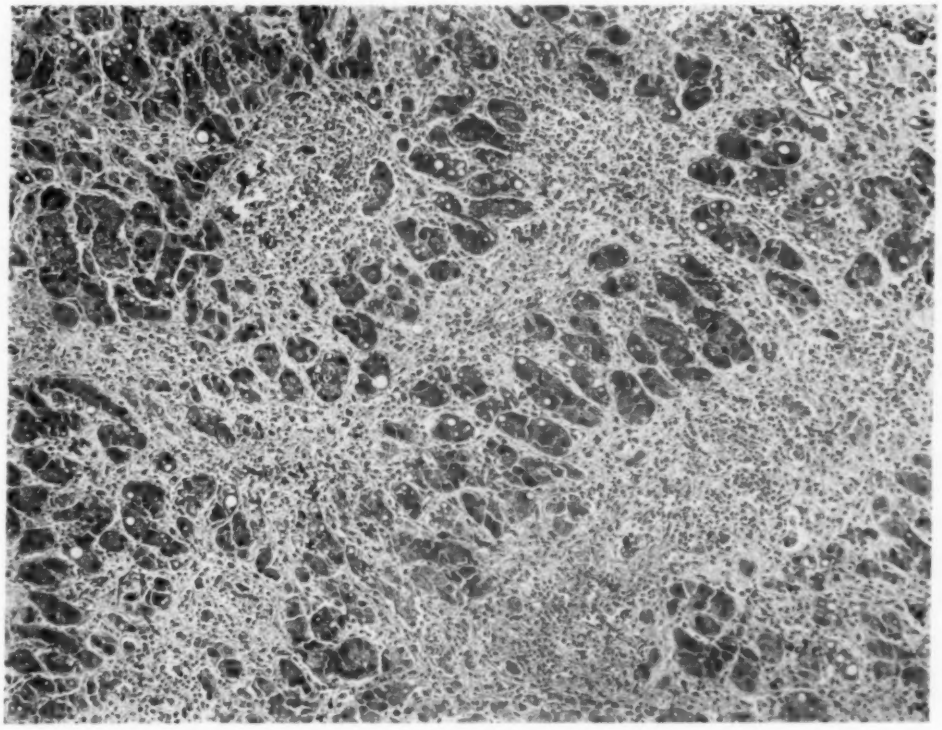

FIG. 2. Section of liver stained with Masson stain (low power).

Autopsy revealed, as was expected, an old rheumatic mitral heart disease, with moderate enlargement of the heart and some pericardial adhesions. Upon the chronically diseased anterolateral mitral leaflet there was a recent extensive ulcerating endocarditis. The spleen was moderately enlarged and two large yellow infarcts were present. The liver weighed 1360 grams but looked smaller than normal; it had a mottled granular surface. Nothing noteworthy was found in the gall-bladder or common duct. Microscopic examination by Professor Balduin Lucke led to the following report: The liver architecture is distorted with separation of the parenchyma into islands by loose strands of connective tissue, particularly around the interlobular biliary canals. In the meshes of this connective tissue are many lymphocytes and polymorphonuclear leukocytes. Some of the bile ducts are normal but others show inflammatory changes, still others have undergone proliferation. In certain areas entire lobules of liver parenchyma have been lost; elsewhere regeneration has replaced the degenerated tissue. The final picture is the result of degeneration, regeneration and overgrowth by inflammatory fibrous tissue and justifies the diagnosis cholangeitis and pericholangitic cirrhosis. In the inflammatory foci in sections stained with Giemsa's solution there were found occasional paired cocci, probably streptococci.

Discussion

This case obviously raises some interesting speculations for some of which, unfortunately, the answers are lacking. It would seem, perhaps, to be the type of case to which the diagnosis cholangeitis lenta would be applied by those who use this term. Such cases are, however, not peculiarly rare, but in this patient there happened to exist an old valvulitis to which the streptococcic infection spread, thus establishing in this patient two conditions to which the term " lenta " might perhaps be applied although the endocarditis here was due to beta hemolytic streptococci. Possibly the chronic venous engorgement incident to the mitral heart disease predisposed this patient to a localization of infection in the liver which, in turn, acted as a focus from which the infection spread to the heart valve. This coincidence would seem to make this case unique unless Eppinger's inclusion of the word endocarditis among the septic manifestations of cholangeitis lenta refers to such a picture, which seems doubtful.

As was said before, the term is not important but it would appear that the concept is and that it deserves more recognition in this country. It is probable that at present such cases are not being recognized and are being confused with catarrhal jaundice, suppurative cholangeitis secondary to gall stones or duct obstruction, or with so-called biliary cirrhosis.

It would seem that the syndrome of primary streptococcal cholangeitis should be accepted, that its " lenta " nature should be recognized. Its potentialities are several—it may act as a focus of infection, giving perhaps what was formerly termed biliary rheumatism—it may continue until the picture of biliary cirrhosis results—or it may act as a source of bacteremia with secondary localization if local conditions favor this—as occurred in this case in which previous rheumatic disease permitted the streptococcus to establish endocarditis as well as the original cholangeitis—two conditions to which the term " lenta " has been applied.

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HEREDITARY HEMORRHAGIC TELANGIECTASIS OCCURRING IN SIX GENERATIONS *

By William Waters Teahan, M.D., *Holyoke, Massachusetts*

Hereditary hemorrhagic telangiectasis, as found in more than six generations of an English family, is a rarity of interest. This condition may be sometimes overlooked because the general practitioner is not familiar with it as an entity.

Osler [1] described a series of three cases in 1901 and commented on an additional case reported by Rendu in 1896. Since then this condition has been called the Rendu-Osler disease. In 1907, Osler [2] wrote that telangiectatic areas in the skin increase as age advances, and that in the young such telangiectases are often temporary in character. He also noted that telangiectatic areas were associated with cirrhosis of the liver and with early internal malignant growths.

Hurst and Plummer,[3] in 1932, reported that the literature at that time contained but 57 family trees in which there was indisputable proof of the disease.

Larrabee and Littman [4] suggest that the following three postulates should be satisfied in order to establish the diagnosis:

1. A positive family history.
2. Telangiectatic areas typical in distribution, character and number.
3. A definite tendency for such spots to bleed.

In reviewing the first rule above, it must be said that either men or women may have the disease and that both sexes may transmit it to their offspring. Fitzhugh [5] reported that one generation often is skipped only to have the disease appear insidiously in the next. He states that this occurred seven times in 212 cases. In some of such instances a very mild type of the disease may have been overlooked in the generation which was apparently "skipped."

The distribution, number and character of the telangiectatic areas are important. They may occur anywhere on the external surfaces of the body or on any of the various mucous membranes. On the skin they are more commonly found on the cheeks, nasal orifices, lips, ears, neck, scalp, fingers and trunk. The mucosa of the nasopharynx is seemingly most often affected, followed in frequency by the tongue, palate, inner cheek, pharynx, larynx, stomach, colon, bladder and brain. Lesions in the stomach, colon, bladder and brain are extremely rare.

Associated anomalies have been recorded. Fitzhugh [6] has reported splenic and hepatic enlargement. Perhaps the increase in size of these organs may be

* Received for publication May 22, 1937.
From the First Medical Service, Rhode Island Hospital.

due to angiomas which have expanded within them. The case described below had an easily palpable mass projecting from the liver.

Given a clinical picture fulfilling the postulates as listed above, one can feel fairly certain of the diagnosis. One must bear in mind, however, that practically everyone has telangiectatic areas on some parts of the body which usually have escaped detection because they produce no symptoms.

The lesions are most often described as small red or purple spots, usually of pin point size, though sometimes larger, and even, in certain rare instances, of spider-like configuration. The lesions may or may not disappear on pressure. Sometimes they may come and go in crops without apparent reason.

Bleeding is variable. Sometimes there is profuse hemorrhage, which in some reported cases has caused death. Fitzhugh [6] reports that in families known to have the disease, he found a mortality of 4 per cent from hemorrhage. Usually there is only a moderate bleeding tendency, which may cause secondary anemias and considerable incapacity from nasal and oral hemorrhage, difficult to check. Such bleeding occurring in the rectum, bladder, larynx and stomach, may account for some of the so-called "idiopathic hemorrhages" that have been described in the past. Trauma is not necessary, for bleeding occurs spontaneously without injury or irritation. Some cases have nasal hemorrhage three or four times daily for weeks at a time. It is Steiner's [7] opinion that bleeding occurs first and that the telangiectatic areas appear only after the initial hemorrhage.

One should be cautious in diagnosing the disease in childhood. Usually the bleeding is not noted until the age of 12 or 14 and if one examines younger children of families whose parents have the disease, they may or may not show telangiectatic areas. On the other hand Weber [8] has reported a case of telangiectasia, not hereditary in origin, which first began to appear on the skin and mucous membranes at 67 years of age. Hereditary cases have histories of having no "spots" on their face until 12 or 16 years of age and having them then appear gradually and later start bleeding. Meikle [9] has stated that the maximum development of these lesions tends to occur in the fourth decade.

The differential diagnosis of hereditary hemorrhagic telangiectasis is not a difficult problem. The disease is unlike hemophilia in that it appears in women, is transmitted by both sexes and not by women only, and is not characterized by delayed coagulation time. Thrombocytopenic purpura should not be confused with telangiectasia because in the former one finds a greatly reduced platelet count, delayed bleeding time, normal clotting time, absence of clot retraction and a positive capillary fragility test. It is well to emphasize that all blood studies are normal in hereditary hemorrhagic telangiectasia unless there is secondary anemia from blood loss.

Meikle [9] considers subacute bacterial endocarditis in differential diagnosis because in both conditions one may have to deal with an ill patient with a café au lait complexion, pyrexia, a variable number of hemorrhagic spots on the lips, conjunctivae and fingers, and splenomegaly. The history of the development of the telangiectases, the characteristic morphology of these lesions, as well as the normal cardiac findings and lack of blood stream infection should clearly differentiate these conditions.

Studies on the histopathology of the disease have been conducted by Hanes [10] and by Steiner.[7] The dilated walls of the affected vessels are composed of but one layer of endothelium and are covered by an extremely thin layer of epi-

dermis or mucosa. There is no elastic layer in such dilated vessels, and hence once a hemorrhage does commence there is little power of the walls to contract.

Numerous therapeutic measures have been instituted; observers vary as to their efficacy. Houser,[11] of Philadelphia, on the basis of a large experience concludes that the chromic acid bead is the most effective local therapy. He finds

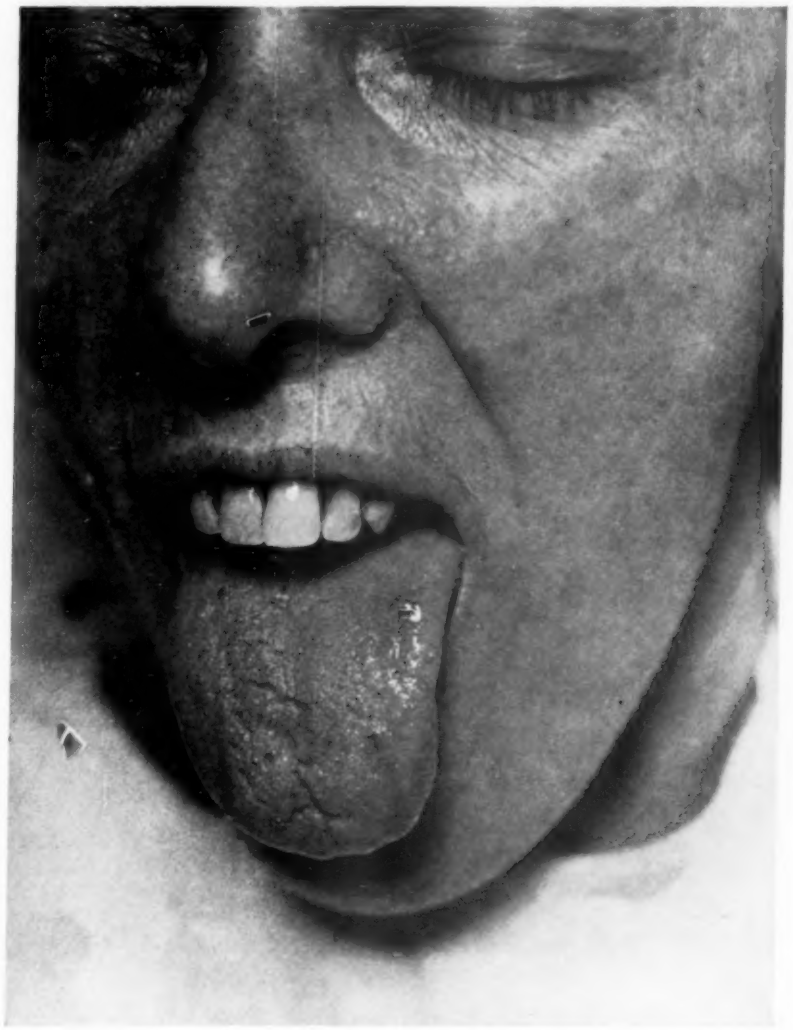


FIG. 1. Telangiectases on tongue and upper lip.

that new areas may appear on essentially normal mucosa after cauterization has been used. His results were not as good with radium, roentgen-ray, electrocoagulation or galvanocautery as with chromic acid bead treatment. He advocates general measures such as high vitamin diet, iron, liver, and rest when needed. Fitzhugh[6] has found that patients with hereditary hemorrhagic telangiectasis, who have Moss type IV blood, are intolerant to transfusion, and this

is more marked in patients with hepatomegaly and splenomegaly. Two cases out of a series of four with the above findings died of severe transfusion reactions associated with post-transfusion jaundice.

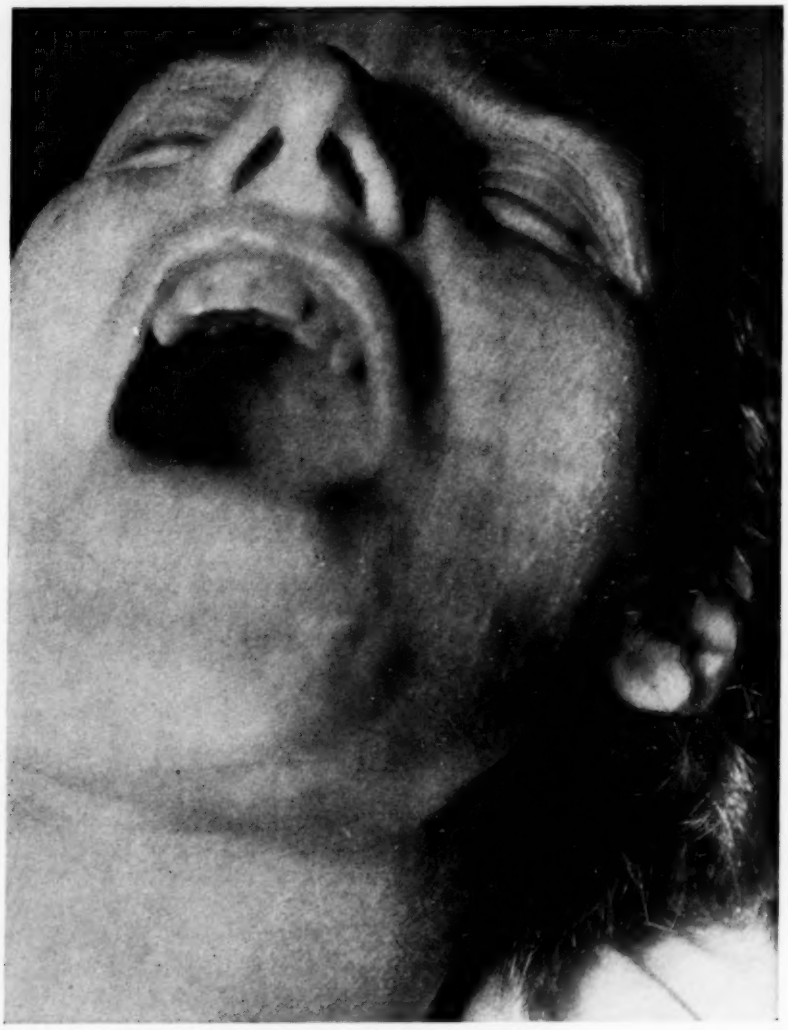


FIG. 2. Telangiectases on palate.

Cases with a genuine family history are prone to have about a 4 per cent mortality due to uncontrolled epistaxis. If sufficiently severe, bleeding will cause secondary anemias with resultant decreased resistance, which in turn may precipitate various infections. The disease may be said to be more severe in the ages between 40 and 50 and thereafter a decrease in bleeding is to be expected.

CASE REPORT

Mrs. Emma H., aged 45, entered the Rhode Island Hospital on September 21, 1936 with three chief complaints, nose bleeds, psoriasis and arthritis. She had had

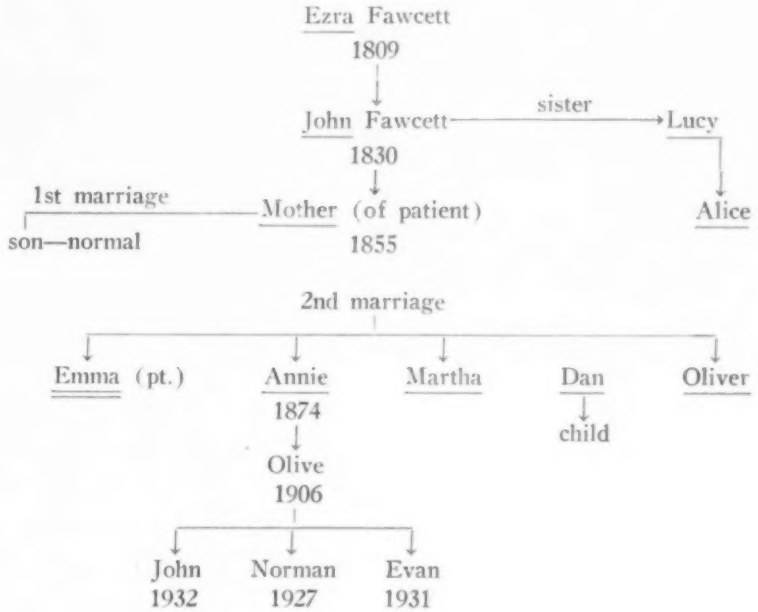
epistaxis ever since she was 16 years old and the bleeding had gradually increased in severity with her age. On admission each hemorrhage might last as long as two days and continue constantly during the day and night. The patient also bled from the mouth on rare occasions. The nasal bleeding tended to recur every few days and often an interval of two weeks might intervene. The slightest trauma or coryza would precipitate attacks. Bleeding also might come without any precipitating symptoms or signs. Lately after spells of bleeding the patient complained of marked dyspnea and weakness and some slight ankle edema. The patient treated her hemorrhages with cotton immersed in hydrogen peroxide; this gave poor results.

The psoriasis was of 19 years' duration, and had decreased in severity. The lesions were on the extensor surfaces of her arms, knees, ankles, thighs and also on her back. None of the many past dermatological treatments benefited the patient.

Eight years ago arthritis affected her left hip; soon it progressed to the right hip, knees, feet and finally her hands and fingers were involved. Her knees had been from time to time red and warm and her ankles on occasion had been black. The arthritis was aggravated by damp weather. About a year and a half ago, the patient seemed cured of all joint involvements and at that time she had no limitation of movement. There was on admission some swelling and stiffness in her knees and a rather numb feeling was usually present.

Past History: The patient stated she had been weak all her life. Historical review of the head, eyes, ears, sinuses, mouth, teeth, throat, larynx, nose, urinary, cardiac and respiratory systems was negative except for the present illness. The patient had anorexia for years and lately vomited after nosebleeds. No blood was noticed in the vomitus. Otherwise, the gastrointestinal system was negative. Her menses began at 13 and her menstrual flow was usually scanty, without pain or intermenstrual discharge. She denies any venereal disease. There were no neurological symptoms. She had never been pregnant.

Family History: The family tree outlined here will serve to simplify this part of the history.



The informant was Annie, sister of the patient. Annie very dramatically told how her mother, in bygone days, tried to reconcile her children to their fate and impressed upon them that their affliction was known, in their family history, as the *Fawcett Marks*. Some folk in the countryside believed that the Fawcett family were disfigured because one of their ancestors committed a grave sin.

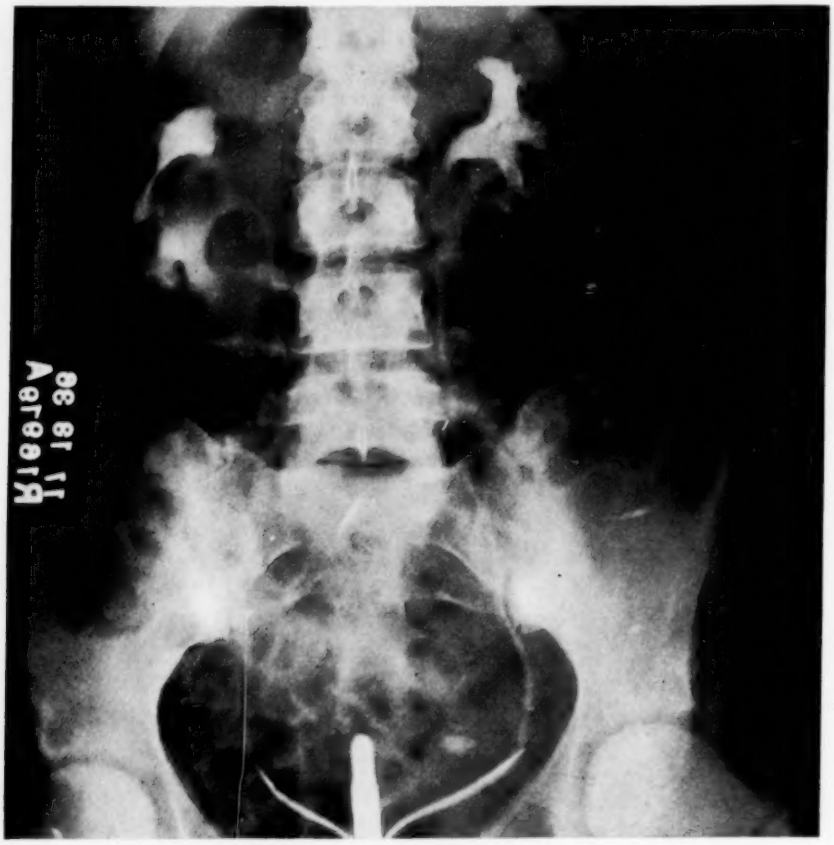


FIG. 3. Retrograde pyelogram showing tumor in right kidney.

This family are natives of Yorkshire, England. Many of their relatives still live there. In the *first* and *second generation* Ezra and John Fawcett are known to have spots on their faces. John's sister Lucy had her face rather severely disfigured by red spots. In the *third generation* her daughter Alice's cheeks were markedly disfigured. John's daughter who was the patient's mother "bled wickedly" for over 40 years. She subsequently died of "cancer of the liver." Sometimes she bled two or three times a day. It was not uncommon for her to bleed daily for weeks at a time from her cheeks and lips. She was married twice. In the *fourth generation* her first marriage resulted in one child who was perfectly normal. Her second marriage, however, resulted in seven children, five of whom were afflicted with this disease. Emma, our patient, has been discussed. Annie has been handicappd because of her telangiectasia. Her lesions are located in back of her ears, on both cheeks, in both nasal folds, on the neck, several large red spots on the tongue, two on her finger tips and a few on her scalp. When she was younger she had numerous spontaneous hemorrhages

from the scalp and face, and on one occasion there was a pulsating hemorrhage from the right nasal fold. These would occur spontaneously whether at rest or work. Martha bled from the lip and tongue, when younger. The many spots on Dan's nose and cheek frequently hemorrhaged. Oliver died "probably from lack of blood" when he was 20 years of age and he "bled terribly like his mother." In the *fifth generation*

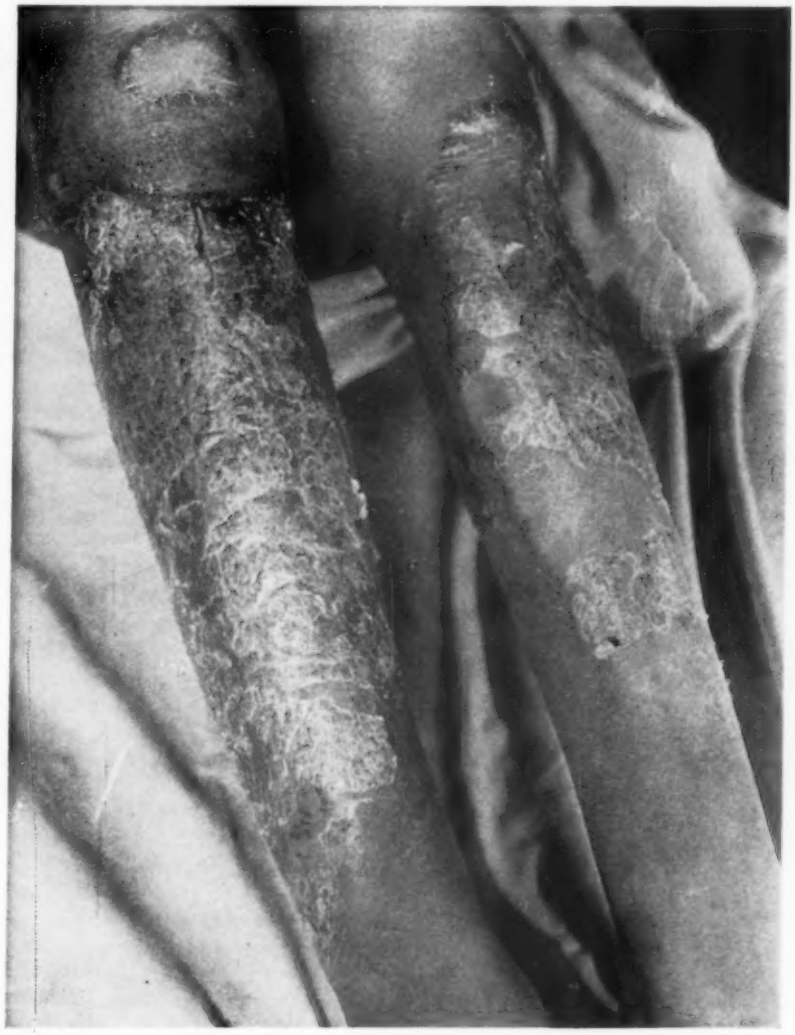


FIG. 4. Psoriasis on legs.

Olive had many nose bleeds after she was 14 and only recently had she failed to be troubled. She had no visible telangiectatic spots when examined. In the *sixth generation* Norman, her oldest boy, bled easily and abnormally from the nose and had one red spot in the nasal fold, none elsewhere. John and Evan had no bleeding, but both had a telangiectatic red spot on the mucosa opposite the last molar tooth and Evan had a spot on the right cheek.

Physical Examination: The patient was a weak, slightly emaciated woman. She

had prominent eyes and café au lait color of her skin. There was no cyanosis, jaundice or orbital edema. On her face were a few diffuse blemishes. The right pupil was slightly irregular, the left was round. Both reacted to light and on accommodation. The extra-ocular muscles were normal as were the fundi. The nasal mucosa was a bright reddish-pink color. There were numerous, injected, bright red areas in the right and left nasal fossa about two mm. in diameter. The turbinates were not swollen. One in the left nasal fossa was stellate. On the edge and in the center of the tongue there were red spots, pin-head size, and not especially raised above the surface. The roof of the mouth had three similar areas, but larger, two to three mm. in diameter. The tonsils were large and cryptic. The lungs were entirely negative except for a few fine crackling râles at both bases. Pulse was 125, blood pressure 140 systolic and 88 diastolic. There was no cardiac enlargement, no precordial thrills or heave. A soft, blowing, systolic murmur was heard over the apex transmitted to the aortic area. The abdomen was full, round and soft. The kidneys and spleen were not palpable. A hard, tongue-shaped mass, about 5 cm. wide and 9 cm. long, was felt in the right upper quadrant and seemed to be connected with the liver. This mass was a bit to the right of the mid-line and descended with respiration. Rectal and vaginal examinations were negative.

The skin had psoriatic lesions over all the extensors: white scales which chipped, and these were on top of hard, dry, raised, cracked areas. There was slight to moderate swelling of all the joints and some limitation of movement in the knees and hands with corresponding decrease in strength. The reflexes were normal. There was no general glandular enlargement.

Laboratory: The hemoglobin was 60 per cent. The red blood cell count was 3.7 million, and the red blood cells were pale. The white blood cell count was 5.2 thousand, and the platelets 210 thousand. The differential count was polymorphonuclears 85 per cent, eosinophiles 1 per cent, lymphocytes 13 per cent, monocytes 1 per cent. The mean corpuscular volume was 100.7. The Wassermann was negative. The blood urea nitrogen was 16 mg., sugar 91 mg., calcium 9 mg. and the sedimentation rate was 10 minutes. The fragility was .36–.30. Coagulation time 1 minute 20 seconds, bleeding time 1 minute 15 seconds. The patient's blood was classified as Group II (Moss).

Stools were positive for occult blood. The urine was essentially negative. Fluid from the right knee was withdrawn and numerous pus cells but no organisms were seen on smear. Cultures demonstrated fine slender unidentified gram negative rods. Guinea pig inoculation was negative. Two subsequent taps were negative to cultural growths. The electrocardiogram was not remarkable.

On October 19, 1936, the roentgen-ray examination of the chest showed clear lung fields. The heart and great vessels were not enlarged.

On September 25, 1936, the roentgen-ray department reported an area of increased opacity on the right side of the abdomen extending from the inferior surface of the first lumbar vertebra down to the iliac crest which might be due to an enlarged kidney or tumor. There was a group of irregular dense shadows above the right sacro-iliac region and these were attributed to calcified glands.

On November 13, 1936, a retrograde kidney examination was done. The bladder urine had very few pus cells, no organisms were seen, no tubercle bacilli were found and there was a sterile culture. The kidney urine revealed a few red blood cells on both sides, also sterile cultures and no organisms or tubercle bacilli were seen by smear. Phenolsulphonephthalein gave a three minute appearance time with 60 per cent concentration on the right side in 30 minutes, a four minute appearance time and 20 per cent reading on the left. Pyelograms showed some displacement of the dye with a large area of increased radiability in the pelvis of the right kidney which was ascribed to tumor. There was dilatation and blunting of the calices. The left kidney pelvis and calices showed no lesion. There was increased density of the bone in the region of both sacro-iliac articulations.

On November 24, 1936, the urology department concluded that there was a growth in the right kidney and that function of the left kidney was very poor. It was the consensus of opinion that operation was inadvisable and that deep roentgen-ray therapy on the right side would be in order.

Treatment: The telangiectatic areas were treated with numerous applications of chromic acid beads and much improvement was noted and bleeding decreased markedly. "Feosol," an iron preparation, and liver extract were given for the anemia. Hemoglobin and red blood cells increased from findings on admission to 96 per cent and 4.7 million on discharge. The white count never varied from around 5.6 thousand. The sedimentation rate lengthened to two hours and nine minutes. The urine was always negative. With the exception of an elevated temperature (101°) and increased pulse rate during the first 10 days, the clinical chart was normal.

The dermatologists treated the psoriasis with "sulisocol" intravenously in the hope it would benefit the arthritis. Diathermy and gentle massage were advised by the orthopedists and were of value.

Result: The patient was discharged on November 24, 1936. There was marked improvement in her general health and appearance. There was only an occasional spotting of blood from the nose. The psoriasis was slightly improved and the arthritic manifestations were greatly benefited.

Summary

Hereditary hemorrhagic telangiectasia is briefly traced through six generations. Literature, differential diagnosis, and treatments are discussed. One case is reported in detail.

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TREATMENT OF PNEUMOCOCCIC MENINGITIS (TYPE XV) WITH PARA-AMINO-BENZENE-SULFONAMIDE

(REPORT OF A CASE WITH RECOVERY) *

By E. T. LISANSKY, M.D., and R. H. PEMBROKE, JR., M.D., *Baltimore, Maryland*

THIS case report attempts to present further [15, 16] evidence concerning the efficacy of sulfanilamide in pneumococcic meningitis. That sulfanilamide and its derivatives are of definite value in the treatment of streptococcic [1, 2, 3, 4, 5, 6] and meningococcic meningitis [7] has been proved by thorough experimental work and frequent clinical findings. The value of sulfanilamide in the treatment of various types of pneumococcic infections is as yet undetermined. However, recent reports in the literature suggest that this drug may be of value in the treatment of type III pneumococcic infections,[8, 9, 10, 11, 12, 13, 14] and is more definitely of value in certain types of pneumococcic meningitis.[15, 16, 21] Its relative value in comparison with sulfapyridine is in process of determination in many clinics.

Available statistics bear witness to the fact that pneumococcic meningitis has heretofore been associated with a very high rate of mortality.[15, 16, 17, 18, 19]

CASE REPORT

E. T., a 22 year old white male, an engineer by profession, was admitted to Mercy Hospital on March 1, 1938 to the private rhinological service of Dr. Waitman F. Zinn. He complained of pain and swelling of the right side of the face, extreme headache, and malaise.

Past History: He had been suffering with recurring head colds and headaches for the entire winter, and on February 24, 1938 (the first day of his illness), he developed an acute right maxillary sinusitis which manifested itself by pain and swelling of the entire right side of the face and extreme headaches. He was seen by his family physician who referred him on February 28 to Dr. W. F. Zinn. At this time the patient was quite ill. Local swelling had increased to such an extent that the right eye had swollen shut. A trocar puncture was done through the right nasal cavity which produced much thick purulent material. Unfortunately, a culture of this purulent material was not taken at this time. The next day irrigation of this antrum was attempted, but was unsuccessful because of the increased viscosity of the material. The patient's general condition seemed much worse and hospitalization was advised.

Physical Examination: This patient presented himself as a well developed, well nourished, young adult male who complained of pain and swelling of the face and extreme headache. He moaned continuously and seemed very toxic. He was very disinclined to answer questions; however, when sufficiently urged he answered intelligently. The entire right side of the face was swollen causing his right eye to be tightly closed. There was marked local elevation of temperature and extreme tenderness of the entire right side of face. The pupil of the left eye reacted to light and accommodation. Extra ocular movements were normal but caused some complaint of pain on the part of the patient. Examination of the ears was negative. The mucous membrane of the nose was swollen so as to entirely occlude the breathing spaces. There was only a small amount of tenacious discharge from the right nasal cavity. A smear taken at this time of this material revealed streptococci, staphylococci, and various other organisms. The mouth was rather dry and sordes were

* Received for publication April 29, 1938.

present on the teeth. The pharynx was injected, and showed some evidence of post-nasal drip. There were a few slightly enlarged tender lymph nodes on both sides of the neck. Transillumination of the sinuses revealed marked clouding of the right maxillary antrum. There was no suggestion of cervical rigidity. Chest expansion was ample and equal on both sides. Percussion note over the lung fields was resonant throughout and the breath sounds were normal. The respirations were regular, rather deep and were 17 per minute. The heart outline was within normal limits. The heart sounds were angry and the rate was 100 per minute. The radial arteries seemed very leathery, the pulse was bounding but regular. The blood pressure was 110 systolic and 70 diastolic. The abdomen was entirely negative. The extremities were negative. Deep and superficial reflexes were entirely normal. There were no pathological reflexes. There were no petechiae or skin rash. Oral temperature was 99.4° F.

Admission Laboratory Findings: The blood picture revealed hemoglobin 17.8 grams or 104 per cent; red blood cells 4,850,000; white blood cells 10,000. The differential count showed 67 per cent segmentocytes, 10 per cent staff forms, 11 per cent lymphocytes, and 12 per cent monocytes. The admission urine specimen showed albumin 3 plus, 10 leukocytes per high power field and 1 erythrocyte. A blood culture was taken at this time which subsequently proved to be negative. Sedimentation rate (Wintrobe) registered 30 mm. per/60 minutes revealing marked acceleration. Blood sugar was 114; urea 35; and urea-N 17 mg. per cent.

Clinical Course: On the afternoon of admission the patient began to complain of recurring attacks of chilliness and his temperature rose to 101° F.

Therapy was instituted consisting essentially of forcing fluids, sedation, and sulfanilamide grains 10, four doses daily. Details of subsequent sulfanilamide dosage and blood and spinal fluid concentrations will be found in table 1. The next day, March 2, the patient's condition was unchanged except for increased toxicity and increasingly severe headache which caused him to moan continuously. His maximum temperature was 101.8° F. at 4 a.m. Irrigation of the right antrum was attempted and a small quantity of purulent material was washed out. It was quite evident that the sinus was not draining favorably. Another blood culture was done which also proved to be negative subsequently. Throughout the entire night and early hours of the morning of March 3, the patient tossed restlessly, and it was necessary to give pantopon frequently in order to produce even slight sedation. Early that morning he complained of pain in the posterior cervical region and increasing headache. He described this headache as a tight band of pressure which encircled the horizontal circumference of the head. By mid-day he was semistuporous. He complained bitterly of photophobia, and divergent strabismus was noticeable. His neck was retracted and examination revealed definite cervical rigidity. Kernig's sign was positive bilaterally. Babinski's sign was positive bilaterally, and Brudzinski's sign was negative. The deep reflexes were very hyperactive and equal. The respirations were of the Cheyne-Stokes type, and the pulse showed a slight irregularity (pulse 64 per minute during apnea and 80 per minute in the dyspneic phase). The eye grounds revealed slight papilledema. The maximum temperature was 103.4° F. He vomited six to ten times during this day.

Because of these findings a lumbar puncture was done which revealed very cloudy fluid with some fibrinous threads. The pressure was 340 mm. water. The cell count was 5,560 per cu. mm., predominately polymorphonuclears (78 per cent). A direct smear of this fluid (centrifuged) revealed no organisms but culture for 12 hours produced definite growth on blood agar. This was found to be a gram positive diplococcus which upon subsequent examination proved to be a pneumococcus. Repeated typing revealed this organism to be type XV pneumococcus.* Retyping was

* Identified by culture upon blood agar, solubility in bile and by Neufeld's quellung reaction using Lederle's rabbit serum.

done 10 to 15 times on subsequent spinal punctures and all results corroborated the initial finding that the organism involved was the pneumococcus type XV. The patient's headache was somewhat relieved by this initial lumbar puncture.

In view of these findings the sulfanilamide was increased to grains 60 per 24 hours and 250 c.c. of 25 per cent glucose were given intravenously twice daily. Lumbar punctures were performed two to three times daily. Details of the spinal fluid findings are recorded in table 1.

TABLE 1

Date	Sulfanilamide Dosage/24 hrs.	Concentration		Pressure	Spinal Fluid Cell Count	Culture	Max. Temp.	Remarks
		Blood	C. S. Fluid					
3/1	40 grains	—	—	—	—	—		
3/2	40 grains	—	—	—	—	—		Blood cult. neg.
3/3	40 grains	—	—	340 mm.	5,560	pos. pneumo. XV	103.4° F.	
				140 mm.	4,200	pos.		
3/4	60 grains	2.5 mg. %	2.5 mg. %	140 mm.	4,050	pos.	101.4° F.	Blood cult. neg.
				200 mm.	1,800	pos.		
3/5	120 grains	6.2	4.0	190 mm.	1,000	pos.	100.2° F.	
				200 mm.	550	pos.		
3/6	120 grains	10.0	7.0	240 mm.	2,220	pos.	103° F.	Radical antrum
				230 mm.	2,000	pos.		
				270 mm.	1,400	pos.		
3/7	120 grains	13.1	9.6	250 mm.	350	pos.	101.2° F.	
				210 mm.	400	pos.		
				190 mm.	320	pos.		
3/8	120 grains	12.9	10.0	210 mm.	340	pos.	103.4° F.	
				300 mm.	2,492	pos.		
				180 mm.	1,160	pos.		
3/9	120 grains	11.4	7.1	150 mm.	801	NEGATIVE	101° F.	
				190 mm.	1,120	NEGATIVE		
3/10	120 grains	10.7	5.0	150 mm.	320	pos.	101° F.	
				120 mm.	115	pos.		
3/11	120 grains	14.3	—	150 mm.	43	NEGATIVE	101.2° F.	
3/12	120 grains	—	—	NO TAP	—	—	100.4° F.	
3/13	80 grains	—	—	NO TAP	—	—	100° F.	
3/14	60 grains	6.2	4.4	150 mm.	29	NEGATIVE	100° F.	
3/15	35 grains	5.0	—	NO TAP	—	—	100° F.	
3/16	discontinued	3.1	—	NO TAP	—	—	100° F.	
3/17		—	—	NO TAP	—	—	100° F.	
3/18		—	—	95 mm.	11	NEGATIVE	99.6° F.	
3/19—4/2				NO TAPS				
4/2/38	DISCHARGED							

All sulfanilamide given per os. One grain sodium bicarbonate given for every grain of sulfanilamide.
On each occasion of positive culture pneumococcus type XV recovered.
Queckenstedt normal on every occasion.
All temperatures on this chart are rectal temperatures.

March 4. The patient's general condition seemed slightly better. He rested at times during the night. His headache which had been eased by the initial lumbar puncture returned to a certain degree. The daily maximum temperature dropped to 101.4° F. The spinal fluid cell count dropped during this day from 4,050 cells per cu. mm. to 1800 cells per cu. mm. Respiration and pulse were regular during some periods of the day. March 5. The patient rested rather quietly during the early hours of the morning and continued clinical improvement was noticeable. Pulse and respiration were regular during the greater part of the day. He ceased moaning and his headache was slightly eased. The cervical rigidity decreased. Kernig's sign could not be elicited as easily as on previous examination. The daily maximum temperature dropped to 100.2° F. Spinal fluid cell count dropped from 1,000 to 550 during this day although the pressure remained about 200. The differential spinal fluid cell count revealed 70 per cent polymorphonuclears. Complete blood count was as follows: Hemoglobin 89 per cent or 15.2 grams; erythrocytes 4,500,000; leukocytes 16,900 per cu. mm. The differential white blood cell count showed 71 per cent segmentocytes, 7 per cent staff forms, 15 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophiles. A blood culture was taken which subsequently proved to be negative.

On this day, the blood sulfanilamide concentration being only 6.2 mg. per cent in the blood, the fluids were restricted to 2,500 c.c. per day in an effort to increase concentration by decreasing volume of urinary output. The sulfanilamide dosage was increased to 120 grains a day. An indirect blood transfusion of 300 c.c. was given.

March 6. On this day his general clinical condition was slightly worse. He began to moan again at intervals and complained of pain in his legs. His headache had returned to a severe degree. Marked photophobia was present. At times slight disorientation was noticeable. His daily maximum temperature rose to 103° F. His spinal fluid cell count rose to 2,200 cells per cu. mm. and the pressure increased to 240 mm. of water. Roentgen-ray of the sinuses revealed marked cloudiness of the right maxillary sinus.

In view of these findings and the continued positive cultures of the spinal fluid, it was considered advisable to drain the right antrum by a radical approach. Dr. Waitman F. Zinn performed the operation using a basal avertin anesthesia and local nerve blocks. No free purulent material was obtained but the sinus was lined with a very thick coagulated mucopurulent exudate which was removed. The sinus was then packed with iodoform gauze. Culture from this sinus produced a *Staphylococcus aureus* and a few chains of diplococci which could not be separated and grown as a pure culture. The patient tolerated the operation well and was returned to his room in good condition.

March 7. The patient rested quietly almost the entire day and his general condition seemed much better. His cervical rigidity had decreased to a minimum and Kernig's sign was negative. He seemed slightly brighter and his irritability was markedly decreased. His maximum temperature was 101.2° F. Spinal fluid cell count was 350 per cu. mm. Spinal fluid pressure was 250 mm. water. Sulfanilamide concentration rose to 13.1 mg. per cent in the blood and 9.6 mg. per cent in the cerebrospinal fluid. The patient showed marked cyanosis which was attributed to the sulfanilamide. A complete blood count was as follows: Hemoglobin 80 per cent; erythrocytes 4,650,000; leukocytes 12,050. A differential white blood cell count revealed 60 per cent segmentocytes, 16 per cent staff forms, 7 per cent lymphocytes, and 8 per cent monocytes. A second blood transfusion of 300 c.c. was given.

March 8. The patient was more restless than on previous day and complained again of the severe headache. His temperature rose to 103.4° F. No other clinical change was noticeable. The spinal fluid cell count increased again to 2,492 cells and the spinal fluid pressure rose to 300 mm. of water.

March 9. The patient seemed very much improved. He rested quietly throughout most of the day and when awake seemed very bright. His headache was considerably eased. The maximum daily temperature was 101° F. The spinal fluid cell count was 801 cells and pressure was 150 mm. water.

The spinal taps done on this day produced the first negative cultures thus far.

March 10. Clinical improvement continued. Mental attitude improved, and the patient began to take a small amount of nourishment by mouth. Maximum temperature was 101° F. Maximum cerebrospinal fluid cell count was 320 cells per cu. mm., and maximum cerebrospinal fluid pressure was 150 mm. of water. The two spinal taps done on this day produced positive cultures but from this time on subsequent spinal taps were entirely negative.

March 11. The patient was very cheerful and alert. He welcomed conversation. He began to take nourishment in more ample quantity. He spent a very comfortable day. Cerebrospinal fluid cell count and pressure continued to drop.

March 12. Continued clinical and laboratory improvement.

March 18. The patient's clinical appearance continued to progress steadily towards recovery. Maximum temperature 99.6° F. Cerebrospinal fluid cell count

revealed 11 cells, all of which were lymphocytes. The cerebrospinal fluid pressure was 95 mm. of water. The culture was negative. This was the last spinal tap done and marked the sixth day of consecutive negative spinal fluid cultures.

March 30. Patient up per routine.

April 2. Patient discharged. No residua of meningeal signs or right maxillary sinus infection evident.

We consider it of importance to note that following the operation which consisted of a right radical antrum, the patient showed a marked improvement in clinical and laboratory findings. There was one return of rise in temperature and spinal fluid cell count which, however, was not accompanied by any marked return of untoward clinical symptomatology; temperature-pulse chart and laboratory findings progressed gradually but steadily towards normal. On March 8 the eighteenth day after admission, the patient's condition had progressed to the point where there were no clinical signs of meningitis and no subjective complaints. The patient left the hospital walking on April 2.

Comments

Josephine Neal et al.[17] in 1934 presented an analysis of 623 cases of meningitis other than meningococcic and tuberculous varieties. Two hundred and fourteen or 34 per cent of these cases were of the pneumococcic variety. In this series of 623 cases of various types of meningitis, 16 cases recovered. It is of importance to note that although they state specifically those varieties which recovered, the pneumococcic variety is not included in this list. In 1935 Josephine Neal[18] reported 24 recoveries from meningitis (other than meningococcic) seen by her staff within the preceding 25 years. Pneumococcic meningitis was not among those varieties treated successfully. The same author[15] in a more recently written article (1938) intimates that she has experienced 100 per cent mortality in pneumococcic meningitis prior to the adoption of sulfanilamide as a therapeutic agent in this disease. In the article just mentioned, the authors reported 14 cases of pneumococcic meningitis. Types of pneumococcus listed were I, III, IV, V, VI, VII, XIII, XIX, and XXXI. All 14 cases received sulfanilamide therapy. When specific serum was available it was given in addition to the sulfanilamide. Of the 14 cases, three recovered. The bacteriological types of pneumococcic meningitis to recover were types IV, XIX, and XXXI. None of these cases received serum. The three cases which recovered followed operative procedure on sinus or on otitic infections. This limited series of cases resulted in 21 per cent cures and 79 per cent fatalities. It is of significance to note that their previous figures concerning pneumococcic meningitis resulted in no cures and 100 per cent fatalities.[17, 18] Basman[16] reported three cases of pneumococcic meningitis treated with sulfanilamide. One of these cases (Type V) recovered. This is the first recorded case of recovery at St. Louis Children's Hospital.

The case which we are reporting is one of type XV pneumococcic meningitis. We have been unable to find record of any other case of type XV pneumococcic meningitis. We have been unable to find any literature concerning the effect of sulfanilamide on type XV pneumococcic infections.

It is necessary to note that in our case a culture of the purulent material removed at operation from the right maxillary sinus revealed a great pre-

dominance of staphylococci and a few diplococci which could not be separated and grown in pure culture. In view of this finding we take the liberty to quote Josephine Neal [17, 18]: "It should be understood that meningitis associated with a definite focus that is apparently primary is not necessarily secondary to it. Not infrequently we see cases of meningococcic meningitis following a pneumonia or otitis media which in all probability are not due to the meningococcus. A recent case of meningitis caused by the hemolytic streptococcus occurred during convalescence from a pneumococcus type II pneumonia." This same author [17] indicates that about 34 per cent of the cases of pneumococcic meningitis which she observed up to 1934 followed infection of the mastoid area, paranasal sinuses, or middle ear. These are the most frequent foci of infection and routes of initiation of pneumococcic meningitis. However, it is also interesting to note that in this same series of cases it was observed that 23 per cent had no evidence of any primary infection elsewhere in the body.

In order of frequency of the bacteriologically etiological variety of meningitis, the meningococcus is the first; the tubercle bacillus second; the streptococcus and the pneumococcus rank third, having about the same degree of incidence. Josephine Neal [18] reported 3,178 cases of meningitis which she classified according to bacteriological etiology. The meningococcus was the offending organism in 1,358 or 42 per cent of the cases, the tubercle bacillus was the offending organism in 986 or 31 per cent of the cases. The streptococcus was found in 238 cases of 7.4 per cent, and the pneumococcus was found in 235 or 7.3 per cent of the cases. The general reliability of this statistical study is borne out by the reports of various other authors.

It is interesting to note that after the age of 20,[18] the incidence of pneumococcic meningitis was 38 per cent. This figure is relatively high for this age group as compared with other types of meningitis with the possible exception of the streptococcic variety. Our case concerned a 22 year old male.

It is necessary to mention that there have been cases recorded of pneumococcic meningitis which have recovered spontaneously with only supportive treatment, occasionally aided by continued spinal punctures. These cases have been so few that their incidence does not alter the available statistics which vouch for the known high mortality rate of pneumococcic meningitis.

Recent reports seem in general to indicate that sulfanilamide is not very effective in the treatment of pneumococcic pneumonia in man.[19] However, experimental work shows rather conclusively that the pneumococcic organism, both in vivo and in vitro, is susceptible to a certain degree to the action of sulfanilamide.[9, 10, 11, 12, 13, 20]

Summary

Pneumococcic meningitis is a disease associated with a very high mortality rate. There have been recent reports in the literature which indicate that sulfanilamide will play an important rôle in reducing this mortality rate. A case of type XV pneumococcic meningitis complicating a right antrum sinusitis which recovered when treated by sulfanilamide and radical drainage of the sinus is reported.

Conclusion

Sulfanilamide therapy associated with radical drainage of foci of infection if present, we believe, is of definite value in the treatment of pneumococcic meningitis. The comparative value of sulfapyridine is in process of determination.

We wish to acknowledge thanks to Dr. Waitman F. Zinn for his permission to report this case, and to Dr. Perrin H. Long for his helpful guidance and advice in the preparation of this report.

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EDITORIAL

PROGRESS IN ADRENAL CORTICAL HORMONE THERAPY

Thomas Addison's description (1855) of a clinical syndrome (morbus addisonii) which resulted from destruction of the adrenal glands first called attention to the vital function of these organs. Shortly thereafter Brown-Sequard (1856) demonstrated conclusively that complete removal of both adrenals was followed promptly by death of the experimental animal. The studies of Vulpian, Oliver, Schaeffer, Abel, Takamine and Aldrich ultimately resulted in the isolation of epinephrin from the adrenal medulla. However, treatment with epinephrin was ineffective in controlling the signs and symptoms of adrenal insufficiency. It was also observed experimentally that the complete removal of one adrenal, accompanied by destruction of the medulla of the remaining adrenal, did not give rise to the signs and symptoms of adrenal insufficiency. From these observations it appeared that the "life-maintaining" substance liberated by the adrenal was derived from the cells of the cortex.

In 1927 Hartman et al.[1] and Rogoff and Stewart[2] independently reported the preparation of adrenal cortical extracts which were capable, on injection, of prolonging the survival period of adrenalectomized animals. In 1930, Swingle and Pfiffner,[3] and Hartman and Brownell,[4] described methods of preparing adrenal cortical extracts of much greater potency. These extracts appeared to be capable of maintaining bilaterally adrenalectomized dogs and cats in good condition for prolonged periods. It was also noted that injections of these extracts in adequate quantities resulted in great improvement in patients with Addison's disease.[5, 6] However, difficulties encountered in the preparation of large quantities of potent extract and in the standardization of the hormone, in addition to the high cost of the preparation, greatly limited adequate clinical trial. Thus at the Mayo Clinic, between the years of 1930 and 1933, Snell[7] noted that the expected length of life of patients with Addison's disease was only slightly prolonged, although marked and continued improvement was observed in some patients following treatment with adrenal cortical extract. During this period it was known that adequate hormone therapy for a moderately severe case of

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Addison's disease might cost $1,000 or more annually. It was apparent that although further improvements might be made in the extraction of the hormone from the glands it was doubtful whether the preparation of hormone from this natural source would ever provide adequate quantities at a cost which most patients could afford.

The classical studies of Loeb et al.[8] and Harrop et al.,[9] demonstrated the beneficial effect of sodium salts in the treatment of patients with Addison's disease, and it was evident that in the clinical evaluation of adrenal cortical hormone therapy, the mineral content of the diet must be considered carefully. Not only was a diet of high sodium content beneficial, but later work (Truszkowski and Zwemer,[10] Wilder et al.[11]) demonstrated the beneficial effect of a low potassium intake in adrenal insufficiency.

In 1933 both Kendall [12] and Grollman [13] obtained crystalline material from adrenal cortical extracts. This material appeared to possess cortical hormone-like activity. Somewhat later Reichstein [14] isolated a crystalline compound from the adrenal cortex which possessed cortical hormone-like activity and which he identified and named "corticosterone." Subsequently Kendall demonstrated the identity of his active compound with that of Reichstein's "corticosterone."

In 1937 Steiger and Reichstein announced the synthesis of a steroid compound, desoxy-corticosterone acetate, from stigmasterol.[15] This compound was found to possess cortical hormone-like activity [16] and was noted to be very closely related, chemically, to progesterone, a sex hormone secreted by the corpus luteum. During the following year Reichstein and Von Euw [17] succeeded in isolating desoxy-corticosterone from adrenal cortical extract, thus establishing its natural occurrence. It is unique that in this instance a hormone was synthesized prior to its isolation from a natural source. It appears probable that desoxy-corticosterone is one of a group of closely related steroid compounds which possess cortical hormone-like activity.

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The close chemical relation between desoxy-corticosterone (21-hydroxy-progesterone, a compound having a high degree of activity as measured by its ability to maintain adrenalectomized animals in good condition) and progesterone, a female sex hormone, is of great interest. The similarity in the clinical picture produced by certain tumors of the adrenal cortex and by arrhenoblastomata of the ovary is well known. Furthermore it has been shown recently [18] that injections of crystalline progesterone result in a retention of sodium and chloride, and an increased renal excretion of potassium. This effect is quite similar to that observed following injections of adrenal cortical hormone.[16] It is also of interest to note that the lives of adrenalectomized animals have been prolonged by injecting large doses of progesterone.[19] No other sex hormone appears to be of any benefit in prolonging the survival of adrenalectomized animals. It thus appears that not only are the adrenal cortical hormone and progesterone closely related chemically but there is also some overlapping in the physiological effects of these compounds.

Intramuscular injections of synthetically prepared desoxy-corticosterone acetate have been shown to be extremely useful in the treatment of patients with Addison's disease.[20] Treatment with desoxy-corticosterone acetate was associated with an increase in body weight, an elevation of blood pressure, increase in plasma volume, a restoration of the plasma concentrations of sodium, chloride and potassium to normal levels, a positive sodium and chloride balance, an increased renal excretion of potassium and inorganic phosphorus, and improved muscular strength. Desoxy-corticosterone acetate treatment was also associated with some improvement in carbohydrate metabolism as measured by a return of the glucose tolerance test to normal.[21] However, in most patients the fasting blood sugar levels remained low despite continued hormone therapy. No striking changes were observed in the pigmentation of patients treated with synthetic hormone.

Desoxy-corticosterone appears to be the most active of the crystalline compounds thus far isolated from the adrenal cortex as measured by the quantity necessary to maintain adrenalectomized animals. The potency of this compound in promoting the storage of glycogen in the liver,[22] and in preventing the development of muscular fatigue under certain experimental conditions,[23] is less than that of other closely related steroid com-

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pounds obtained from the adrenal cortex. It also appears as though adrenal cortical extracts may contain compounds of much greater activity than those thus far isolated.[12]

The synthesis of desoxy-corticosterone provides for the first time an adequate quantity of crystalline adrenal cortical hormone for clinical use. The uniformity of the preparation, and the constancy of potency are of inestimable value, but not more important than is the fact that the synthetic compound provides adequate therapy at a greatly reduced cost.

Recently a method has been described,[21] whereby prolonged hormone therapy may be obtained by implanting subcutaneously tablets of crystalline desoxy-corticosterone acetate in patients with Addison's disease. This method is an application of the experimental studies of Deanesly and Parkes who obtained a prolonged hormone effect when crystals of sex hormones were implanted in the subcutaneous tissues of suitable animals.[25] In preparing a patient for the implantation of pellets, it is essential to determine beforehand the dose of synthetic hormone in oil, injected intramuscularly once daily, which is necessary for satisfactory maintenance. From the daily hormone requirement, the number of tablets (100–150 mg. each) necessary to provide adequate substitution can then be calculated. The hard tablets of synthetic hormone, being only slightly water soluble are absorbed slowly and provide a supply of hormone for several months. They have been removed from time to time, and since no binding substance is used, an accurate measure of the amount of hormone absorbed was ascertained simply by drying and then weighing the tablets. It was found that over a period of several months there was an almost uniform rate of absorption. No untoward local reaction occurs about the tablets. This method of therapy offers several advantages in that daily injections of hormone are obviated, the absorption of hormone occurs at a much more constant rate, and a considerable economy in hormone is effected (approximately 30 per cent) as compared to the hormone required when single daily intramuscular injections of hormone are employed.

It is to be noted, however, that whereas aqueous extracts of adrenal cortex can be given in almost unlimited quantities with no apparent untoward reaction the marked sodium chloride retaining property of desoxy-corticosterone acetate permits the development of edema and hypertension when the hormone is administered in excess, particularly when added sodium chloride therapy is given simultaneously.

The synthesis of desoxy-corticosterone acetate marks a new step in the study of the hormone of the adrenal cortex and in the treatment of patients with Addison's disease. The uniform potency of the preparation will be of inestimable aid in controlling adequate therapy. The subcutaneous implantation of pellets of hormone offers a very advantageous method of administering hormone where long continued therapy is necessary.

G. W. THORN

REVIEWS

Adventures in Respiration: Modes of Asphyxiation and Methods of Resuscitation. By YANDELL HENDERSON. 316 pages; 21 × 14.5 cm. The Williams & Wilkins Company, Baltimore. 1938. Price, $3.00.

To the average internist this will be both a stimulating and a disturbing book. It attacks his conceptions of acidosis, its definition, its mechanism, and the validity of the usual methods of measuring it. In return it leaves him with a new theory which is rather difficult to grasp. The inner relationship of oxygen deficiency to carbon dioxide deficiency has not yet been solved.

The book is to some extent historical, even autobiographical in its approach, since it tells the story of the growth of our knowledge of respiration over 30 years during which the author has been working in this field. In this time he has registered many successes and of course a few failures. We owe to him the widespread acceptance of inhalations of carbon dioxide and oxygen as an indispensable aid in resuscitation from asphyxia and in postoperative depression. His chapter on the use of the same remedy in pneumonia reveals that he is not yet willing to concede that in this condition it has proved a failure.

A disadvantage of the book is that while the author's opponents are brilliantly attacked and his own position interestingly stated there are not enough data furnished to enable a careful reader to form his own opinion. It would seem helpful, too, to the general scientific public, for whom the book seems to have been written, if the author would somewhere clearly state just what his own definition of acidosis is and give us some factual basis for the intriguing phrase "the flight of alkali to the tissues."

In spite of the confusion it induces in the uninitiated, no physician can fail to be attracted by the enthusiasm of the author, nor by his persuasiveness, his ingenuity, and the modest story of his frequent triumphs.

M. C. P.

Outline of Psychiatric Case-Study. By PAUL W. PREU, M.D. 140 pages; 19 × 13 cm. Paul B. Hoeber, Inc., New York City. 1939. Price, $1.85.

This outline seems essentially an expansion of the well-known, standard Kirby and Cheney Guide. Dr. Preu indicates most of the questions he considers necessary to obtain adequate information about an individual. He very wisely stresses the importance of putting things down in the terms actually used by the patient and the informant—not the historian's retrospective impression of what was said.

The observations on history-taking technic (pp. 4–6) and method of mental examination (pp. 74–76) are good, although we do feel that the mental examination should contain only items directly observed at that time by the examiner (p. 81).

Too much stress is laid on school record as a criterion of intelligence. We should like to have seen a section on the examination of uncoöperative patients included. We dislike the use of such obscure terms as "anancasm" (none of our dictionaries listed it).

It is very easy to read. Like most guides, it should be most useful in making the historian think about things he wants to know about a well studied case. Its skeleton outlines for practical use (no one could possibly sit down with it at a history-taking session) are a little lost in the mass of questions. It is a good guide for institutional beginners. But we wish someone, sometime, would devise a satisfactory outline of mental examination for non-psychotic, office and general hospital patients.

H. M. M.

The Avitaminoses. By WALTER H. EDDY, Ph.D., and GILBERT DALLDORF, M.D. 338 pages; 23.5 × 15.5 cm. The Williams & Wilkins Company, Baltimore. 1937. Price, $4.50.

The book plans to be a helpful manual rather than a complete treatise on the avitaminoses and it well fulfills its purpose. The clinician will find an authoritative statement of the nature of the vitamins and of their function. Rapid changes in this field have already added many new facts not available when the book was published but this small volume will long remain a valuable basic text for the internist.

M. C. P.

Diseases of the Nervous System in Infancy, Childhood, and Adolescence. By FRANK R. FORD, M.D. 939 pages; 25.5 × 16.5 cm. Charles C. Thomas, Springfield, Illinois. 1937. Price, $8.50.

This volume of 939 pages appeared two years ago but has not previously been reviewed in this journal. It has stood the test of these years in which it has been frequently used as a reference book. It is a careful scholarly type of work of unusual completeness, clearly written, practical, and illustrated by numerous case histories. To the internist and pediatrician it is a great source of help in a field which cannot be sharply separated from their own. This help will be particularly in the clinical descriptions of the disease entities and in the discussions of diagnosis. Treatment is often dealt with rather briefly and sometimes without the specific details which a practitioner craves. The well chosen references will be of great assistance. Those who have not used this text will be well repaid if they learn to consult it.

M. C. P.

Manual of Toxicology. By FORREST RAMON DAVISON, M.B., M.Sc., Ph.D. 241 pages; 19 × 13.5 cm. Paul B. Hoeber, Inc., New York City. 1939. Price, $2.50.

This manual cannot be commended. The clinical effects of the chief poisons have been very inadequately and often incorrectly described. The therapeutic procedures are vaguely indicated, so that no safe application of the measures advocated could be deduced. Many important therapeutic measures are omitted. Minor disadvantages are the frequent misspelling of words and the incompleteness of the index.

C. A.

COLLEGE NEWS NOTES

The New 1939 Directory of the College

By October 1 a new and completely revised Directory of the American College of Physicians will be ready for distribution. It includes the names of 1 Master, 2969 Fellows and 1234 Associates; total 4204. The contents of the Directory include Officers and Regents, past Officers, past Boards of Regents, Board of Governors, Committees, a historical statement concerning the College, the Constitution and By-Laws, Directory of Life Members and statement concerning the Endowment Fund, record of Awards and Fellowships, Geographic Roster of all members, Alphabetical and Biographical Roster of all members and a directory of Deceased Members. This book is used extensively as a directory of competent internists and allied specialists on the North American Continent. All members of the College in good standing receive the Directory complimentary, as a part of their memberships. Members with waiver of dues, because of age limit or retirement from practice because of illness or other reasons, may obtain copies of the Directory at the prepublication price of $1.25 postpaid. The Directory is not sold for commercial purposes. However, it is frequently complimented to libraries, Deans of Medical Schools, to Research organizations and to Municipal, State and National scientific bodies.

1940 Annual Session of the College

The Twenty-fourth Annual Session of the American College of Physicians will be held in Cleveland, Ohio, April 1–5, inclusive, 1940, with General Headquarters at the Municipal Auditorium and Hotel Headquarters at the Statler Hotel.

Exceptionally fine facilities are available at the hotels, the auditorium and in the hospitals. Cleveland groups and institutions, including Western Reserve University School of Medicine, are placing all facilities at the disposal of the College.

The programs for the General Sessions and the Special Lectures are in charge of the President of the College, Dr. O. H. Perry Pepper, 36th & Spruce Sts., Philadelphia, Pa. All requests and suggestions for papers on the General Sessions program, or on the Lecture Program, should be addressed to President Pepper. The program of Clinics and Round Tables is under the direction of the General Chairman, Dr. Howard T. Karsner, Institute of Pathology, Western Reserve University, Cleveland, Ohio. The Technical Exhibits and General Business Management of the Session will be under the direction of the Executive Secretary, Mr. E. R. Loveland, 4200 Pine St., Philadelphia, Pa.

Dr. David P. Barr, F.A.C.P., St. Louis, was a guest speaker before the 47th Annual Meeting of the Idaho State Medical Association at Boise, August 23–26, his subjects being "Influence of the Pituitary Gland on Bodily Function and Disease"; "Clinical Management of Lobar Pneumonia"; "Vitamins and Their Clinical Importance"; "Diagnosis and Treatment of Parathyroid Disease."

Dr. James D. Bruce, F.A.C.P., President-Elect of the American College of Physicians and Vice President in charge of Postgraduate Medical Education of the University of Michigan Medical School, and Dr. Stuart Pritchard, F.A.C.P., Director of the W. K. Kellogg Foundation, Battle Creek, are among members of the newly formed Michigan Poliomyelitis Commission to arrange consultation service for the

early diagnosis and prompt orthopedic care of patients in the recent outbreak of infantile paralysis. The Commission received $10,000 from the Michigan State Medical Society, Michigan Crippled Children's Commission, Michigan Society for Crippled Children, the Children's Fund, the Kellogg Foundation and the Wayne County Board of Auditors. The State was organized into sixteen districts in which consultation service was maintained. County, State and District Health Officers acted as clearing agents in obtaining consultants. The Presidents of County Medical Societies arranged for the service in those counties that do not have full-time health service. Eighty-six cases were reported the first ten days in August, sixty-two of these being in Detroit.

A recent announcement from New York University College of Medicine contains advice of the following faculty promotions:

Dr. Currier McEwen, F.A.C.P.
Dr. Elaine P. Ralli, F.A.C.P.
Dr. William Goldring, F.A.C.P.
Dr. Norman H. Jolliffe, F.A.C.P.

promoted to Associate Professors of Medicine;

Dr. Morris Block (Associate)
Dr. Marshall S. Brown, Jr. (Associate)

promoted to Assistant Professors of Clinical Medicine.

Among guest speakers on the program of the Fifth Annual Piedmont Postgraduate Clinical Assembly at Anderson, S. C., September 19–21, were the following members of the College:

Dr. Kenneth M. Lynch, F.A.C.P., Charleston, S. C., "Some Things We Know About Cancer";
Dr. Edgar R. Pund, F.A.C.P., Augusta, Ga., "Ovarian Tumors";
Dr. Virgil P. Sydenstricker, F.A.C.P., Augusta, Ga., "Incomplete Deficiency Syndromes";
Dr. Robert Wilson, Jr., F.A.C.P., Charleston, S. C., "Diabetes and the Use of Protamine Insulin."

Dr. James S. Sweeney, F.A.C.P., Dallas, Texas, was the recipient of the honorary degree of Doctor of Laws at the last commencement of Texas Christian University.

Dr. David B. Snelling (Associate), Montgomery, Ala., has been appointed Health Officer of Choctaw (Ala.) County.

Dr. Gerald B. Webb, F.A.C.P., 2nd Vice President of the American College of Physicians, received the Trudeau Medal of the National Tuberculosis Association at its last Annual Meeting in Boston. Dr. Webb received the award in recognition of his attempts "to produce specific immunity against tuberculosis by the inoculation of animals with very minute numbers of tubercle bacilli."

The Institute of Medicine of Chicago recently announced again the offering of the Joseph A. Capps (F.A.C.P.) Prize of $400 for the most meritorious investigation in medicine, or in the specialties in medicine. Competition is open to graduates of medical schools in Chicago, who have completed an internship, or a year of laboratory work, since the first of 1937. Manuscripts must be submitted to the Secretary of the Institute, 86 East Randolph St., Chicago, Ill., not later than December 31.

Dr. Cyrus C. Sturgis, F.A.C.P., Professor of Internal Medicine and Chairman of that department, University of Michigan Medical School, Ann Arbor, and Dr. John E. Gordon, F.A.C.P., Professor of Preventive Medicine and Epidemiology, Harvard University Medical School, Boston, have been appointed special consultants for the W. K. Kellogg Foundation, Battle Creek.

Dr. William W. Graves, F.A.C.P., Professor of Neuropsychiatry and Director of that department, St. Louis University School of Medicine, has been selected to receive the Award of Merit of the St. Louis Medical Society, "in consideration of the results of his studies on inherited variations in relation to the problems of the human constitution."

Under the Presidency of Dr. Charles E. Sears, F.A.C.P., Portland, the Oregon State Medical Society held its 65th Annual Meeting in Gearhart, September 6–9. Dr. Clifford J. Barborka, F.A.C.P., Chicago, appeared on the program with three addresses:

"Recent Advances in Nutrition";
"Management and Treatment of Obesity";
"Diagnosis and Treatment of Peptic Ulcer."

Dr. Paul H. Ringer, F.A.C.P., Asheville, N. C., and Dr. David O. N. Lindberg, F.A.C.P., Decatur, Ill., have been elected Vice Presidents of the National Tuberculosis Association.

Dr. James Burns Amberson, Jr., F.A.C.P., New York, Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, Okla., and Dr. Benjamin L. Brock, F.A.C.P., Waverly Hills, Ky., have been elected President, President-Elect and Secretary, respectively, of the American Trudeau Society. This Society was organized in 1905 as the American Sanatorium Association, but at its Annual Meeting in Boston in June, its name was changed and its scope and functions expanded. While primarily the membership was made up of physicians associated with sanatoriums, the reorganization provides for inclusion of many physicians outside of sanatoriums, who have active interest in tuberculosis and other diseases of the chest.

OBITUARIES

DR. LOUIS H. FLIGMAN

Dr. Louis H. Fligman of Helena, Montana died July 14, 1939, following an appendix operation performed July 4.

He was born in Rumania in 1878, coming to the United States as a boy. He resided in Minneapolis, where he had his preliminary education, graduating from the University of Minnesota in medicine in 1901. Dr. Fligman moved to Helena, Montana, where his interest in internal medicine and his unusual diagnostic skill soon earned for him a place of enviable distinction which extended well beyond the confines of his own state.

Dr. Fligman became a member of the American College of Physicians February 24, 1920, and a life member in January, 1938; was elected to the Board of Governors in 1925, serving continuously in that capacity until his death. His interest in the College was manifested by consistent attendance of the sessions as well as the Board meetings. He was also a former President of the Montana Medical Association as well as a member and former President of the State Board of Health.

He was attending physician to St. Peter's and St. John's Hospitals, consulting internist to the Veterans Administration Facility, Lieutenant Commander in the Reserve Corps of the United States Navy, Director for the Montana American Society for the Control of Cancer, and was a diplomate of the American Board of Internal Medicine.

His postgraduate studies were pursued with unusual zeal, and on eight occasions he returned to Vienna for postgraduate study. Dr. Fligman was most energetic in the pursuit of outdoor exercise, and was an ardent golfer, being a member of the Helena Town and Country Club. His local interests embraced membership in the Chamber of Commerce and the Mountain Club. A most able and accomplished physician, despite his remoteness from medical centers, he was rarely equipped and qualified to practice internal medicine. His diagnostic skill was exceptional, while his unselfishness and fine standard of ethics were outstanding.

He is survived by his widow; a brother, Mr. Jos. Fligman of Chicago; a sister, Mrs. J. S. Holzman of Helena; and one step-daughter, Mrs. Donald C. McGraw of Summit, N. J.

CHARLES H. COCKE, M.D., F.A.C.P.
Chairman of the Board of Governors, A.C.P.

DR. JAMES FRANCIS RICE

Dr. James Francis Rice, Fellow of the College since 1917 and, therefore, almost a charter member, died on August 3, 1939, at his home in Watertown, N. Y., from a cerebral hemorrhage. He was born in York,

Pa., on September 3, 1872, a son of Rev. Dr. William Henry Rice and Mary Holland Rice. His ancestors were among the early settlers in America and were among the founders of Bethlehem, Pa. He attended Central High School in Philadelphia, Pa. He received his A.B. degree from New York University in 1893 and his A.M. degree from that University in 1895. From 1894 to 1898 he was a teacher at the New York School for the Blind in New York City. He then entered the College of Physicians and Surgeons, Columbia University, from which he was graduated in 1902 with a degree of Doctor of Medicine. From 1902 to 1904 he was an interne in the New York Hospital. He spent some time in service at the Westchester Division of the New York Hospital, then later in 1904 he began his private practice in Buffalo, and continued his practice there until the fall of 1935, when he went to Watertown, where he was on the Associate Staff of both the Mercy Hospital and the House of the Good Samaritan.

Dr. Rice married Miss Grace M. Easterly of Watertown, N. Y., in August 1925. She survives, as does a sister of Dr. Rice, Miss Rebekeh Rice of Randolph, N. Y. He was a member of various medical bodies. While in Buffalo he was from 1921 to 1925 secretary and later from 1930 to 1931 president of the Buffalo Academy of Medicine. He was also a Fellow of the Academy. He was a member of Psi Upsilon fraternity and served as president of the Buffalo Alumni Chapter. He was also a member of the New York State Medical Association and the Jefferson County Medical Society. He had also served as president of the Buffalo Society of Phi Beta Kappa.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York